(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number
WO 2004/087138 A1

(51) International Patent Classification[7]: A61K 31/426, A61P 27/00, 17/00, 11/00

(21) International Application Number: PCT/JP2004/004596

(22) International Filing Date: 31 March 2004 (31.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/458,370 31 March 2003 (31.03.2003) US

(71) Applicants (*for all designated States except US*): **SUCAMPO AG** [CH/CH]; Graben 5, Zug, CH-6300 (CH). **FUJISAWA PHARMACEUTICAL CO., LTD.** [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 5418514 (JP).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **UENO, Ryuji** [JP/US]; 11025 Stanmore Drive, Potomac, Montgomery, MD 20854 (US). **NAGASHIMA, Akira** [JP/JP]; c/o FUJISAWA PHARMACEUTICAL CO., LTD., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 5418514 (JP). **INOUE, Takayuki** [JP/JP]; c/o FUJISAWA PHARMACEUTICAL CO., LTD., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 5418514 (JP). **OHKUBO, Mitsuru** [JP/JP]; c/o FUJISAWA PHARMACEUTICAL CO., LTD., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 5418514 (JP). **YOSHIHARA, Kousei** [JP/JP]; c/o FUJISAWA PHARMACEUTICAL CO., LTD., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 5418514 (JP).

(74) Agent: **TAKASHIMA, Hajime**; Fujimura Yamato Seimei Bldg., 2-14, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410044 (JP).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR TREATING VASCULAR HYPERPERMEABLE DISEASE

(57) Abstract: The present invention provides a method for treating a vascular hyperpermeable disease (except macular edema), which method comprises administering to a patient in need thereof a vascular adhesion protein-1 (VAP-1) inhibitor in an amount sufficient to treat said patient for said disease. The agents are 2-acylamino thiazole compounds.

WO 2004/087138 A1

DESCRIPTION

METHOD FOR TREATING VASCULAR HYPERPERMEABLE DISEASE

TECHNICAL FIELD

The present invention relates to a method for treating a vascular hyperpermeable disease (except macular edema).

BACKGROUND ART

Vascular adhesion protein-1 (hereinafter to be abbreviated as VAP-1) is amine oxidase (semicarbazide sensitive amine oxidase, SSAO) which is abundant in human plasma, and shows remarkably increased expression in vascular endothelium and vascular smooth muscle of the inflammatory region. While the physiological role of VAP-1 has not been clarified until recently, VAP-1 gene was cloned in 1998, and VAP-1 has been reported to be a membrane protein that regulates rolling and migration of lymphocyte and NK cell as an adhesion molecule under regulation of expression by inflammatory cytokine. Although the amine to be a substrate is unknown, it is considered to be methylamine generated in any part of living organisms. It is also known that hydrogen peroxide and aldehydes produced by the amine oxidase activity in a molecule are important factors of adhesion activity.

However, the correlation between the VAP-1 enzyme activity in plasma and vascular permeability has not been heretofore known.

DISCLOSURE OF INVENTION

The present inventors have found that VAP-1 enzyme activity in plasma and vascular permeability are correlated, and therefore, a VAP-1 inhibitor is useful for the prophylaxis or treatment of a vascular hyperpermeable disease (except macular edema) and completed the present invention. Thus, the present invention provides the following.

(1) A method for treating a vascular hyperpermeable disease (except macular edema), which method comprises administering to a subject in need thereof a vascular adhesion protein-1 (VAP-1) inhibitor in an amount sufficient to treat said subject for said disease.

(2) The method of (1), wherein said disease is a disease in mucous membrane.

(3) The method of (2), wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or respiratory tract.

(4) The method of (1), wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic operation, an ocular inflammatory disease caused by a physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis, angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

(5) The method of (1), wherein the VAP-1 inhibitor is a compound of the formula (I) [hereinafter sometimes referred to

as Compound (I)]:

$$R^1—NH—X—Y—Z \quad (I)$$

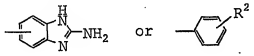
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:



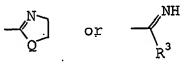
wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$; and

E is optionally protected amino, $-N=CH_2$,



wherein

Q is -S- or -NH-; and

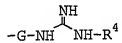
R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

or a derivative thereof;

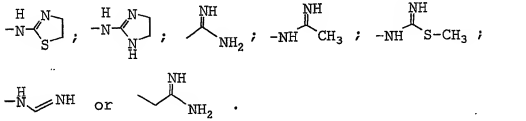
or a pharmaceutically acceptable salt thereof.

(6) The method of (5), wherein, in the formula (I), Z is a group of the formula:

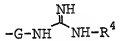
wherein R^2 is a group of the formula:



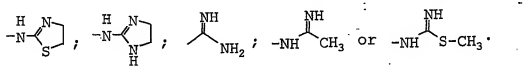
(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



(7) The method of (6), wherein, in the formula (I), R^2 is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



(8) The method of any of (5) to (7), wherein, in the formula (I), R^1 is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl.

(9) The method of (1), wherein the VAP-1 inhibitor is

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(10) The method of (1), wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(11) A pharmaceutical composition for the treatment of a vascular hyperpermeable disease (except macular edema), which comprises, as an active ingredient, a VAP-1 inhibitor.

(12) The composition of (11), wherein said disease is a disease in mucous membrane.

(13) The composition of (12), wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or respiratory tract.

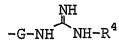
(14) The composition of (11), wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic operation, an ocular inflammatory disease caused by a physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema,

dermatitis, angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

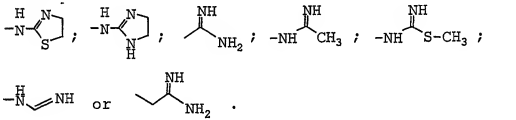
(15) The composition of (11), wherein the VAP-1 inhibitor is Compound (I); or a derivative thereof; or a pharmaceutically acceptable salt thereof.

(16) The composition of (15), wherein, in the formula (I), Z is a group of the formula:

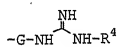
wherein R^2 is a group of the formula:



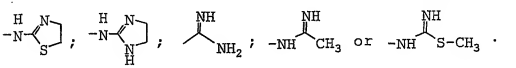
(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



(17) The composition of (16), wherein, in the formula (I), R^2 is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



(18) The composition of any of (15) to (17), wherein, in the formula (I), R^1 is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by

methylsulfonylbenzyl.

(19) The composition of (11), wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(20) The composition of (11), wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(21) A use of a VAP-1 inhibitor for preparing a medicament for the treatment of a vascular hyperpermeable disease (except macular edema).

(22) The use of (21), wherein said disease is a disease in mucous membrane.

(23) The use of (22), wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or respiratory tract.

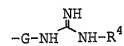
(24) The use of (21), wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy,

neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic operation, an ocular inflammatory disease caused by a physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis, angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

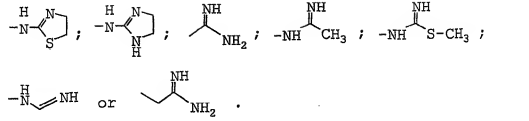
(25) The use of (21), wherein the VAP-1 inhibitor is Compound (I); or a derivative thereof; or a pharmaceutically acceptable salt thereof.

(26) The use of (25), wherein, in the formula (I), Z is a group of the formula:

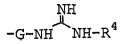
wherein R^2 is a group of the formula:



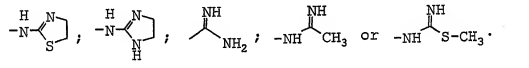
(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



(27) The use of (26), wherein, in the formula (I), R^2 is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



(28) The use of any of (25) to (27), wherein, in the formula (I), R^1 is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl.

(29) The use of (21), wherein the VAP-1 inhibitor is

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(30) The use of (21), wherein the VAP-1 inhibitor is

N-[4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated on the discovery that VAP-1 enzyme activity in plasma and vascular permeability are correlated, and therefore, an inhibitor of vascular adhesion protein-1 (VAP-1; also referred to as semicarbaside sensitive amine oxidase (SSAO) or copper-containing amine oxidase) is effective in treating or ameliorating a vascular hyperpermeable disease (except macular edema). Accordingly, the present invention provides a method for treating a vascular hyperpermeable disease (except macular edema). The "treating a vascular hyperpermeable disease (except macular edema)" and "treatment of a vascular hyperpermeable disease (except macular edema)" are intended to include the administration of a compound having a VAP-1 inhibitory activity to a subject for purposes, which can include prophylaxis, amelioration, prevention and cure of a vascular hyperpermeable disease (except macular edema). As used herein, by the "subject" is meant a target of the administration of VAP-1 inhibitor in the present invention, which is specifically any animal such as human, mouse, rat, swine, dog, cat, horse, bovine and the like, especially human. The vascular hyperpermeable disease (except macular edema), which is to be treated by the method of the present invention, includes the disease caused/accompanied by increased vascular permeability, for example, diseases in mucous membrane such as ocular, cutis, otorhinology, respiratory tract and the like. Examples thereof include diseases in ocular-mucous membrane, such as aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal

edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory diseases caused by bacterial or viral infection, and by an ophthalmic operation, ocular inflammatory diseases caused by a physical injury to the eye and symptoms caused by ocular inflammatory diseases including itching, flare, edema and ulcer; mucocutaneous diseases, such as erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis and angioneurotic edema; and diseases in mucous membrane (e.g., otorhinology, respiratory tract etc.), such as laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis and otitis media.

The method comprises the administration of a VAP-1 inhibitor in an amount sufficient to treat a vascular hyperpermeable disease (except macular edema). Any VAP-1 inhibitor can be used in the method of the present invention as long as it is safe and efficacious. Herein, the "VAP-1 inhibitor" will be used to refer to such compounds and is intended to encompass all compounds that inhibit enzyme activity of VAP-1 at any and all points in the action mechanism thereof.

The VAP-1 inhibitor in the present invention includes, for example, a compound represented by the following formula (I) [Compound (I)]:

$R^1-NH-X-Y-Z$ (I)

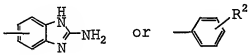
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:

 or

wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$; and

E is optionally protected amino, $-N=CH_2$,

 or 

wherein

Q is -S- or -NH-; and

R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

The definition of each group of Compound (I) is shown in the following.

Suitable "halogen" includes fluorine, chlorine, bromine and iodine.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" includes straight or branched alkyl having 1 to 6 carbon atom(s), such as methyl, ethyl,

propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which more preferred one is C_1-C_4 alkyl.

Suitable "lower alkylthio" includes lower alkylthio containing the above lower alkyl, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, tert-pentylthio and hexylthio.

Suitable "lower alkylene" includes straight or branched alkylene having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, propylene, ethylidene and propylidene, in which more preferred one is C_1-C_4 alkylene.

Suitable "lower alkenylene" includes straight or branched alkenylene having 2 to 6 carbon atom(s), such as -CH=CH-, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, -CH=CH-CH=CH-, $-CH=CH-CH_2-CH_2-CH_2-$, $-CH=CH-CH=CH-CH_2-CH_2-$ and -CH=CH-CH=CH-CH=CH-, in which more preferred one is C_2-C_4 alkenylene.

The above lower alkenylene may be in E or Z form, respectively. Thus, those skilled in the art will recognize that the lower alkenylene includes all E, Z-structures when it has 2 or more double bonds.

Suitable "aryl" includes C_6-C_{10} aryl such as phenyl and naphthyl, in which more preferred one is phenyl. The "aryl" may be substituted by 1 to 3 substituent(s) and the substitution sites are not particularly limited.

Suitable "aralkyl" includes aralkyl wherein the aryl moiety has 6 to 10 carbon atoms [i.e. the aryl moiety is C_6-C_{10} aryl of the above "aryl"] and the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C_1-C_6 alkyl of the above "lower alkyl"], such as benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-phenylpropyl, 4-

phenylbutyl and 5-phenylpentyl.

The "optionally protected amino" means that an amino group may be protected with a suitable protecting group according to a method known *per se*, such as the methods described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like. The suitable "protecting group" includes tert-butoxycarbonyl (i.e., Boc), an acyl group as mentioned below, substituted or unsubstituted aryl(lower)alkylidene [e.g., benzylidene, hydroxybenzylidene, etc.], aryl(lower)alkyl such as mono-, di- or triphenyl-(lower)alkyl [e.g., benzyl, phenethyl, benzhydryl, trityl, etc.] and the like.

Suitable "optionally protected amino" includes amino and tert-butoxycarbonylamino (i.e. -NHBoc).

Suitable "heterocycle" includes "aromatic heterocycle" and "non-aromatic heterocycle".

Suitable "aromatic heterocycle" includes 5 to 10-membered aromatic heterocycle containing 1 to 3 heteroatom(s) selected from nitrogen, oxygen and sulfur atoms besides carbon atom(s), and includes, for example, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyridazine, pyrimidine, pyrazine and the like.

Suitable "non-aromatic heterocycle" includes 5 to 10-membered non-aromatic heterocycle containing 1 to 3 heteroatom(s) selected from nitrogen, oxygen and sulfur atoms besides carbon atom(s), and includes, for example, pyrrolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, dioxolan, oxazolidine, thiazolidine, triazolidine and the like.

Suitable "acyl" includes acyl having 1 to 20 carbon atom(s), such as formyl, alkylcarbonyl, arylcarbonyl,

alkoxycarbonyl and aralkyloxycarbonyl.

Suitable "alkylcarbonyl" includes alkylcarbonyl wherein the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C_1-C_6 alkyl of the above "lower alkyl"], such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and heptanoyl, in which more preferred one is C_1-C_4 alkyl-carbonyl.

Suitable "arylcarbonyl" includes arylcarbonyl wherein the aryl moiety has 6 to 10 carbon atom(s) [i.e. the aryl moiety is C_6-C_{10} aryl of the above "aryl"], such as benzoyl and naphthoyl.

Suitable "alkoxycarbonyl" includes alkoxycarbonyl wherein the alkoxy moiety has 1 to 6 carbon atom(s), such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl and hexyloxycarbonyl, in which more preferred one is alkoxycarbonyl wherein the alkoxy moiety has 1 to 4 carbon atom(s).

Suitable "aralkyloxycarbonyl" includes aralkyloxycarbonyl wherein the aryl moiety has 6 to 10 carbon atom(s) [i.e. the aryl moiety is C_6-C_{10} aryl of the above "aryl"] and the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C_1-C_6 alkyl of the above "lower alkyl"], such as benzyloxycarbonyl, phenethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl and 5-phenylpentyloxycarbonyl.

Suitable "bivalent residue derived from thiazole" of the "bivalent residue derived from optionally substituted thiazole" includes

 and  .

The "thiazole" may have 1 to 3 substituent(s) and the substitution sites are not particularly limited.

Suitable "substituent" of the above "optionally substituted thiazole" includes, for example,

(1) halogen which is as defined above;

(2) alkoxycarbonyl which is as defined above, such as ethoxycarbonyl;

(3) optionally substituted aryl, which aryl is as defined above and the substitution sites are not particularly limited, such as phenyl and 4-(methylsulfonyl)phenyl;

(4) a group of the formula: $-CONR^aR^b$ wherein R^a is hydrogen, lower alkyl, aryl or aralkyl and R^b is hydrogen, lower alkyl, aryl or aralkyl, wherein the lower alkyl, aryl and aralkyl are as defined above, such as N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl and N-benzylaminocarbonyl;

(5) a group of the formula: $-CONH-(CH_2)_k-$aryl wherein k is an integer of 0 to 6; the aryl is as defined above, which may have 1 to 5 substituent(s) selected from the group consisting of $-NO_2$, $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above, $-CF_3$ and -O-aryl wherein the aryl is as defined above, and the substitution sites are not particularly limited;

(6) a group of the formula: $-CONH-(CH_2)_m-$heterocycle wherein m is an integer of 0 to 6; the heterocycle is as defined above, such as pyridine;

(7) a group of the formula: -CO-heterocycle wherein the heterocycle is as defined above, such as pyrrolidine, piperidine, piperazine, thiomorpholine, which may have 1 to 5 substituent(s) selected from the group consisting of -CO-(lower alkyl) wherein the lower alkyl is as defined above, -CO-O-(lower alkyl) wherein the lower

alkyl is as defined above, $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above, oxo (i.e. =O) and a group of the formula: $-CONR^cR^d$ wherein R^c is hydrogen, lower alkyl, aryl or aralkyl and R^d is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(8) a group of the formula: $-(CH_2)_n$-aryl wherein n is an integer of 1 to 6; the aryl is as defined above, which may have 1 to 5 substituent(s) selected from the group consisting of -S-(lower alkyl) wherein the lower alkyl is as defined above, $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above, $-CO_2-$(lower alkyl) wherein the lower alkyl is as defined above, -NHCO-O-(lower alkyl) wherein the lower alkyl is as defined above and a group of the formula: $-CONR^eR^f$ wherein R^e is hydrogen, lower alkyl, aryl or aralkyl and R^f is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(9) a group of the formula: $-(CH_2)_o$-heterocycle wherein o is an integer of 0 to 6; the heterocycle is as defined above, such as pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, which may have 1 to 5 substituent(s) selected from the group consisting of oxo (i.e. =O); -CO-(lower alkyl) wherein the lower alkyl is as defined above; -CO-O-(lower alkyl) wherein the lower alkyl is as defined above; $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above; -CO-(heterocycle) wherein the heterocycle is as defined above such as pyrrolidine, piperazine and morpholine, which may have 1 to 5 substituent(s) selected from the group consisting of lower alkyl and halogen, wherein the lower alkyl and halogen are

as defined above, and the substitution sites are not particularly limited; and a group of the formula: $-CONR^gR^h$ wherein R^g is hydrogen, lower alkyl, aryl or aralkyl and R^h is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(10) a group of the formula: $-(CH_2)_p-NR^iR^j$ wherein p is an integer of 0 to 6; R^i is hydrogen, acyl, lower alkyl, aryl or aralkyl and R^j is hydrogen, acyl, lower alkyl, aryl or aralkyl wherein the acyl, lower alkyl, aryl and aralkyl are as defined above, and the lower alkyl may have 1 to 5 substituent(s) selected from the group consisting of a group of the formula: $-CONR^kR^l$ wherein R^k is hydrogen, lower alkyl, aryl or aralkyl and R^l is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(11) a group of the formula: -CON(H or lower alkyl)-$(CHR^m)_q$-T wherein q is an integer of 0 to 6; the lower alkyl is as defined above; R^m is hydrogen, aralkyl which is as defined above, or alkyl which is as defined above, which may be substituted by 1 to 3 substituent(s) selected from the group consisting of -OH and $-CONH_2$ and the substitution sites are not particularly limited; and T is hydrogen; a group of the formula: $-CONR^nR^o$ wherein R^n is hydrogen, lower alkyl, aryl or aralkyl and R^o is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above; $-NH-CO-R^p$ wherein R^p is lower alkyl which is as defined above or aralkyl which is as defined above; $-NH-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above; $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above; -heterocycle wherein the heterocycle is as

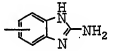
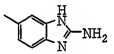
defined above, such as pyridine, pyrrolidine and morpholine, which may have 1 to 3 substituent(s) such as oxo (i.e. =O), and the substitution sites are not particularly limited; or -CO-(heterocycle) wherein the heterocycle is as defined above, such as piperidine and morpholine; and

(12) a group of the formula: $-(CH_2)_r-CO-NR^tR^u$ wherein r is an integer of 1 to 6; R^t is hydrogen, lower alkyl, aryl or aralkyl and R^u is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above.

The substitution site on the aryl or heterocycle is any suitable position thereof, but not particularly limited.

Preferable "substituent" of the above "optionally substituted thiazole" is methylsulfonylbenzyl.

The substitution sites of R^2 on the phenyl in Compound (I) is not particularly limited.

When Z is a group of the formula:  , the substitution sites on the group are not particularly limited.  is particularly preferable.

Any nitrogen atom in the amino (i.e. $-NH_2$), imino (i.e. =NH or -NH-) or the like contained in Compound (I) may be protected according to the methods, which are known to those skilled in the art, such as the methods described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like.

When Compound (I) has an asymmetric carbon atom in the structure, those skilled in the art will recognize that Compound (I) includes all stereoisomers.

For example, the Compound (I) and derivatives thereof, or compounds reported to have inhibited VAP-1 enzyme (SSAO) may include fluoroallylamine derivatives, semicarbazide

derivatives, hydrazide derivatives, hydrazino derivatives, 1,3,4-oxadiazine derivatives, 2,6-diethoxybenzylamine, 2,6-di(n-propoxy)benzylamine, 2,6-diisopropoxybenzylamine, 2,6-di(n-butoxy)benzylamine, 2,6-bis(methoxymethoxy)benzylamine, 2,6-bis(methoxymethyl)benzylamine, 2,6-diethylbenzylamine, 2,6-di-n-propylbenzylamine, 2,6-bis(2-hydroxyethoxy)benzylamine, and the like.

The above compounds can be exemplified as follows.

1) fluoroallylamine derivatives, semicarbazide derivatives and hydrazide derivatives described in WO 93/23023,

2) hydrazino derivatives described in WO 02/02090,

3) 1,3,4-oxadiazine derivatives described in WO 02/02541,

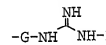
4) 4-alkyl-5-alkoxycarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine derivatives described in WO 02/38153,

5) 2,6-diethoxybenzylamine, 2,6-di(n-propoxy)benzylamine, 2,6-diisopropoxybenzylamine, 2,6-di(n-butoxy)benzylamine, 2,6-bis(methoxymethoxy)benzylamine, 2,6-bis(methoxymethyl)benzylamine, 2,6-diethylbenzylamine, 2,6-di-n-propylbenzylamine and 2,6-bis(2-hydroxyethoxy)benzylamine described in USP 4,888,283.

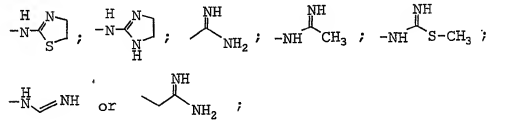
The compounds exemplified in the present invention as a VAP-1 inhibitor and in WO 93/23023 as an SSAO inhibitor, such as those described in Lyles et al. (Biochem. Pharmacol. 36:2847, 1987) and in USP 4650907, USP 4916151, USP 4943593, USP 4965288, USP 5021456, USP 5059714, USP 4699928, European patent application 295604, European patent application 224924 and European patent application 168013, are also encompassed in the VAP-1 inhibitor.

Of the above-mentioned compounds, preferred is Compound (I), more preferably, a compound of the formula (I) wherein Z is a group of the formula:

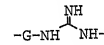
wherein R^2 is a group of the formula:



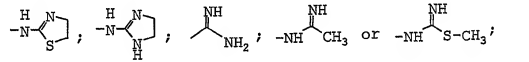
(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



still more preferably, a compound wherein R^2 is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



, and yet more preferably, a compound wherein R^1 is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl and derivatives thereof.

Of the above-mentioned Compound (I), preferable specific compounds include

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (hereinafter Compound A; see Production Example 1),

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (hereinafter Compound B; see Production Example 16),

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-

(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (see Production Example 48),

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (see Production Example 50),

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (see Production Example 58), and

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (see Production Example 110),

particularly N-{4-[2-(4-{[amino(imino)methyl]amino}-phenyl)ethyl]-1,3-thiazol-2-yl}acetamide and derivatives thereof.

The term "derivative" is intended to include all compounds derived from the original compound.

In the present invention, the VAP-1 inhibitor can be administered as a prodrug to a subject. The term "prodrug" is intended to include all compounds that convert to the VAP-1 inhibitor in the body of administration subject. The prodrug can be any pharmaceutically acceptable prodrug of VAP-1 inhibitor. Moreover, the VAP-1 inhibitor can be administered to an administration subject as a pharmaceutically acceptable salt.

The pharmaceutically acceptable salt of VAP-1 inhibitor in the present invention is nontoxic and a pharmaceutically acceptable conventional salt, which is exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

The VAP-1 inhibitor can be also formulated as a pharmaceutically acceptable acid addition salt. Examples of the pharmaceutically acceptable acid addition salts for use in

the pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, hydriodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and arylsulfonic acids, for example, p-toluenesulfonic acid.

As a pharmaceutically acceptable salt of VAP-1 inhibitor represented by the formula (I), a pharmaceutically acceptable acid addition salt such as (mono-, di- or tri-)hydrochloride and hydriodide, particuraly hydrochloride, is preferable.

The above-mentioned VAP-1 inhibitor may be commercially available or can be produced based on a known reference.

Also, Compound (I), particularly Compound A: N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide and Compound B: N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide, can be synthesized according to the Production Method given below.

Those compounds or derivatives thereof that are not commercially available can be prepared using organic synthetic methods known in the art.

The VAP-1 inhibitor or a pharmaceutically acceptable salt thereof can be administered in accordance with the present inventive method by any suitable route. Suitable routes of administration include systemic, such as orally or by injection, topical, periocular (e.g., subTenon's), subconjunctival, intraocular, intravitreal, intracameral, subretinal, suprachoroidal and retrobulbar administrations. The manner in which the VAP-1 inhibitor is administered is dependent, in part, upon whether the treatment of a vascular hyperpermeable disease (except macular edema) is prophylactic or therapeutic.

The VAP-1 inhibitor is preferably administered as soon

as possible after it has been determined that a subject such as a mammal, specifically a human, is at risk for a vascular hyperpermeable disease (except macular edema) (prophylactic treatments) or has begun to develop a vascular hyperpermeable disease (except macular edema) (therapeutic treatments). Treatment will depend, in part, upon the particular VAP-1 inhibitor used, the amount of the VAP-1 inhibitor administered, the route of administration, and the cause and extent, if any, of a vascular hyperpermeable disease (except macular edema) realized.

One skilled in the art will appreciate that suitable methods of administering a VAP-1 inhibitor, which is useful in the present inventive method, are available. Although more than one route can be used to administer a particular VAP-1 inhibitor, a particular route can provide a more immediate and more effective reaction than another route. Accordingly, the described routes of administration are merely exemplary and are in no way limiting.

The dose of the VAP-1 inhibitor administered to the administration subject such as animal including human, particularly a human, in accordance with the present invention should be sufficient to effect the desired response in the subject over a reasonable time frame. One skilled in the art will recognize that dosage will depend upon a variety of factors, including the strength of the particular VAP-1 inhibitor to be employed, the age, species, conditions or disease states, and body weight of the subject, as well as the degree of a vascular hyperpermeable disease (except macular edema). The size of the dose also will be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular VAP-1 inhibitor and the

desired physiological effect. It will be appreciated by one of ordinary skill in the art that various conditions or disease states may require prolonged treatment involving multiple administrations.

Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached.

Generally, the VAP-1 inhibitor can be administered in the dose of from 0.001 μg/kg/day to about 300 mg/kg/day, preferably from about 0.01 μg/kg/day to about 10 mg/kg/day, which is given in a single dose or 2 to 4 doses a day or in a sustained manner.

Pharmaceutical compositions for use in the present inventive method preferably comprise a "pharmaceutically acceptable carrier" and an amount of a VAP-1 inhibitor sufficient to treat a vascular hyperpermeable disease (except macular edema) prophylactically or therapeutically as an active ingredient. The carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration.

The amount of the VAP-1 inhibitor in the composition may vary depending on the formulation of the composition, and may generally be 0.00001 - 10.0 wt%, preferably 0.0001 - 5 wt%, more preferably 0.001 - 1 wt%.

The VAP-1 inhibitor can be administered in various manners to achieve the desired VAP-1 inhibitory effect. The VAP-1 inhibitors can be administered alone or in combination with pharmaceutically acceptable carriers or diluents, the

properties and nature of which are determined by the solubility and chemical properties of the inhibitor selected, the chosen administration route, and standard pharmaceutical practice. The VAP-1 inhibitor may be administered orally in solid dosage forms, e.g., capsules, tablets, powders, or in liquid forms, e.g., solutions or suspensions. The inhibitor may also be injected parenterally in the form of sterile solutions or suspensions. Solid oral forms may contain conventional excipients, for instance, lactose, sucrose, magnesium stearate, resins, and like materials. Liquid oral forms may contain various flavoring, coloring, preserving, stabilizing, solubilizing, or suspending agents. Parenteral preparations are sterile aqueous or non-aqueous solutions or suspensions which may contain certain various preserving, stabilizing, buffering, solubilizing, or suspending agents. If desired, additives, such as saline or glucose, may be added to make the solutions isotonic.

The present inventive method also can involve the co-administration of other pharmaceutically active compounds. By "co-administration" is meant administration before, concurrently with, e.g., in combination with the VAP-1 inhibitor in the same formulation or in separate formulations, or after administration of a VAP-1 inhibitor as described above. For example, corticosteroids, prednisone, methylprednisolone, dexamethasone, or triamcinolone acetinide, or noncorticosteroid anti-inflammatory compounds, such as ibuprofen or flubiprofen, can be co-administered. Similarly, vitamins and minerals, e.g., zinc, anti-oxidants, e.g., carotenoids (such as a xanthophyll carotenoid like zeaxanthin or lutein), and micronutrients can be co-administered.

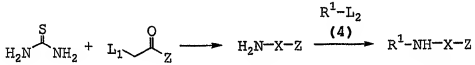
In addition, the present invention provides a use of a

VAP-1 inhibitor for preparing a medicament for the treatment of a vascular hyperpermeable disease (except macular edema).

Production Method of Compound (I)

Compound (I) is prepared in accordance with, but is not limited to, the following procedures. Those skilled in the art will recognize that the procedures can be modified according to the conventional methods known *per se*.

Procedure A: Synthesis of Compound (I) wherein Y is a bond



wherein

L_1 is a leaving group such as halogen (e.g., chlorine, bromine, iodine);

Z is as defined above;

X is as defined above, in this case,  ;

R^1 is acyl; and

L_2 is a leaving group such as -OH, halogen (e.g., chlorine, bromine, iodine), -O-acyl wherein the acyl is as defined above (e.g., -O-acetyl and the like).

Formation of Thiazole Moiety X

Compound (1) is reacted with Compound (2) or its salt to give Compound (3).

Suitable salt of Compound (2) may be the same as those exemplified for Compound (I).

Compounds (1) and (2) or its salt may be commercially available or can be prepared in accordance with the methods known *per se* (see Production Example 11).

The reaction is usually carried out in a conventional solvent such as ethanol, acetone, dichloromethane, acetic acid, and other organic solvent which does not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Compound (3) thus obtained can be isolated or purified by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

Acylation

Compound (3) or its salt is reacted with Compound (4) to give Compound (5). Since R^1 is an acyl group, this reaction is an acylation.

The conventional acylation method may be employed in the present invention.

Compound (4) may be commercially available or can be prepared in accordance with the methods known *per se*.

The reaction is usually carried out in a conventional solvent such as dichloromethane, chloroform, methanol, and other organic solvent which does not adversely affect the reaction, or a mixture thereof.

The reaction is also preferably carried out in the presence of a conventional base such as 4-dimethylaminopyridine, pyridine etc. A liquid base can be also used as the solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Compound (5) thus obtained can be isolated or purified by known separation or purification means, such as

concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

The acylation may be applied to Compound (1) in advance.

The nitrogen atom in Compound (1), (2), (3) or (5) may be protected or deprotected, as necessary, in accordance with methods known *per se* such as the methods described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like.

Procedure B: Synthesis of Compound (I) wherein Y is lower alkylene such as ethylene (i.e. $-CH_2-CH_2-$) or lower alkenylene such as vinylene (i.e. -CH=CH-), for example,

$$\underset{(6)}{R^1\text{-NH-X-CHO}} + \underset{(7)}{L_3\text{-}CH_2\text{-Z}} \longrightarrow \underset{(8)}{R^1\text{-NH-X-CH=CH-Z}}$$

$$\xrightarrow{\text{Reduction}} \underset{(9)}{R^1\text{-NH-X-}CH_2\text{-}CH_2\text{-Z}}$$

wherein

L_3 is a leaving group such as halogen (e.g., chlorine, bromine, iodine); and

R^1, X and Z are as defined above.

Formation of Olefin Compound

Compound (6) or its salt is reacted with Compound (7) or its salt to give an olefin compound (8).

Suitable salts of Compounds (6) and (7) may be the same as those exemplified for Compound (I).

Compounds (6) and (7) or salts thereof may be commercially available or can be prepared in accordance with the methods known *per se* (see Production Example 1 and 3).

The reaction is usually carried out in a conventional

solvent such as N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, and other organic solvent which does not adversely affect the reaction, or a mixture thereof.

The reaction is also usually carried out in the presence of triphenylphosphine and a conventional base such as potassium tert-butoxide, sodium hydride, sodium hydroxide and the like.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Compound (8) thus obtained can be isolated or purified by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

Reduction

Compound (8) or its salt is reduced in accordance with a conventional method to give Compound (9).

The conventional reduction includes hydrogenation, catalytic hydrogenation, etc.

Among others, catalytic hydrogenation is preferable.

The catalytic hydrogenation is carried out in the presence of a catalyst such as palladium carbon, preferably 10% palladium carbon.

The catalytic hydrogenation is usually carried out in a conventional solvent such as tetrahydrofuran, ethanol, ethyl acetate, and other solvent which does not adversely affect the reaction, or a mixture thereof.

The catalytic hydrogenation is also preferably carried out in the presence of a conventional acid such as acetic acid, hydrochloric acid and the like. A liquid acid can be

also used as the solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Compound (9) thus obtained can be isolated or purified by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

Therefore, Compound (11) or a salt thereof can be prepared from Compound (10) or a salt thereof in a similar manner as described above. Suitable salts of Compounds (10) and (11) may be the same as those exemplified for Compound (I).

R^1-NH-X-(lower alkenylene)-Z **(10)**

$$\xrightarrow{\text{Reduction}} \quad R^1\text{-NH-X-(lower alkylene)-Z} \quad \textbf{(11)}$$

The nitrogen atom in Compound (6), (7), (8), (9), (10) or (11) may be protected or deprotected, as necessary, in accordance with methods known *per se* such as the methods described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like.

Procedure C: Synthesis of Compound (I) wherein Y is -CONH-

$$\underset{\textbf{(12)}}{R^1\text{-NH-X-COOH}} + \underset{\textbf{(13)}}{L_4\text{-NH-Z}} \longrightarrow \underset{\textbf{(14)}}{R^1\text{-NH-X-CONH-Z}}$$

wherein

L_4 is a hydrogen atom or a protecting group, which is known *per se*, such as tert-butoxycarbonyl as described in the above "optionally protected amino" (see Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), etc.); and

R^1, X and Z are as defined above.

Amidation

Compound (12) or a reactive derivative thereof, or its salt is reacted with Compound (13) or its salt to give an amidated compound (14).

Suitable reactive derivative of Compound (12) includes an acid halide, an acid anhydride and an activated ester.

The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, hologenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); or an ester with an N-hydroxy compound (e.g., N,N-dimethlhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.). These reactive derivatives can be optionally selected from them according to the kind of

Compound (12) to be used.

Suitable salts of Compound (12) and a reactive derivative thereof as well as Compound (13) may be the same as those exemplified for Compound (I).

Compound (12) and a reactive derivative thereof as well as Compound (13) or salts thereof may be commercially available or can be prepared in accordance with the methods known *per se* (see Production Example 7).

The conventional amidation method may be employed in the present invention.

The reaction is usually carried out in a conventional solvent such as dichloromethane, methanol, ethanol, acetone, tetrahydrofuran, N,N-dimethylformamide, and any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction is also preferably carried out in the presence of a conventional condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N'-dicyclohexylcarbodiimide, N,N'-carbonylbis(2-methylimidazole)triphenylphosphine, and an additive such as 1-hydroxybenzotriazole, 1-hydroxysuccinimide, 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Compound (14) thus obtained can be isolated or purified by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

The nitrogen atom in Compound (12), (13) or (14) may be protected or deprotected, as necessary, in accordance with methods known *per se* such as the methods described in

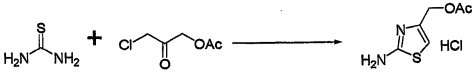
Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like.

The present invention is explained in more detail in the following by way of Production Examples and Examples, which are not to be construed as limitative.

The test compounds used in the Examples were N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (hereinafter Compound A) synthesized in Production Example 1 and N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (hereinafter Compound B) synthesized in Production Example 16.

Production Example 1:

Step 1



A mixture of 3-chloro-2-oxopropyl acetate (5 g) and thiourea (2.5 g) in ethanol (25 ml) was refluxed for 4 hours. The reaction mixture was cooled to ambient temperature and the resulting crystalline precipitate was collected by filtration and washed with ethanol (20 ml) to give (2-amino-1,3-thiazol-4-yl)methyl acetate hydrochloride (3.5 g) as white crystals.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.07(3H, s), 4.92(2H, s), 6.87(1H, s).

MS: 173$(M+H)^+$

Step 2

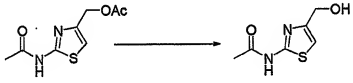
To a mixture of (2-amino-1,3-thiazol-4-yl)methyl acetate hydrochloride (56 g) and pyridine (45 g) in dichloromethane

(560 ml) was added acetyl chloride (23 g) over a period of 30 minutes at 5°C, and the reaction mixture was stirred for 10 minutes at the same temperature. The reaction mixture was poured into water (500 ml) and extracted with chloroform (1 L). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residual solid was collected by filtration with isopropyl ether to give (2-(acetylamino)-1,3-thiazol-4-yl)methyl acetate (47 g) as white crystals.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.12(3H, s), 2.29(3H, s), 5.08(2H, s), 6.93(1H, s).

MS: 215$(M+H)^+$

Step 3

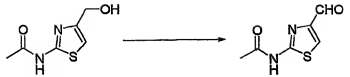


A mixture of (2-(acetylamino)-1,3-thiazol-4-yl)methyl acetate (46 g) and potassium carbonate (30 g) in methanol (640 ml) was stirred for 3 hours at ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was diluted with chloroform, and the insoluble material was filtered off. The resulting solution was purified by flash column chromatography on silica-gel with methanol / chloroform (1/99). The resulted solid was collected by filtration with isopropyl ether to give N-(4-(hydroxymethyl)-1,3-thiazol-2-yl)acetamide (35 g) as white crystals.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 4.44(2H, d, J=5.0Hz), 5.20(1H, t, J=5.0Hz), 6.88(1H, s), 12.02(1H, brs).

MS: 173$(M+H)^+$

Step 4

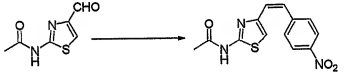


N-(4-(Hydroxymethyl)-1,3-thiazol-2-yl)acetamide (2.8 g) was dissolved in methanol (10 ml) and chloroform (200 ml). Then manganese (IV) oxide (28.3 g) was added to the solution under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 7 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The resulting solid was washed with ethyl ether to give N-(4-formyl-1,3-thiazol-2-yl)acetamide (2.01 g) as an off-white solid.

mp. 195.5-199°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 8.28(1H, s), 9.79(1H, s), 12.47(1H, brs).

Step 5



1-(Bromomethyl)-4-nitrobenzene (1.9 g), triphenylphosphine (2.31 g) and N,N-dimethylformamide (20 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2.5 hours. Then potassium tert-butoxide (1.19 g) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (1.5 g) were added and the mixture was stirred at room temperature for 14 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with 1N-hydrochloric acid, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:1) → (1:2) as an eluent, and triturated with ethyl ether to give N-{4-[(Z)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (1.59 g) as a

yellow solid.

mp. 155-157°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.13(3H, s), 6.64(1H, d, J=12.5Hz), 6.71(1H, d, J=12.5Hz), 7.18(1H, s), 7.79(2H, d, J=9.0Hz), 8.17(2H, d, J=9.0Hz), 12.02(1H, brs).

MS: 290(M+H)$^+$

Step 6

A mixture of N-{4-[(Z)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (2 g) and 10% palladium carbon (400 mg) in methanol (25 ml), tetrahydrofuran (25 ml) and acetic acid (18 ml) was stirred under 4 atm hydrogen at ambient temperature for 5 hours. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate. The organic solution was washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:2) → ethyl acetate as an eluent, and triturated with ethyl alcohol / ethyl ether to give N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (539.6 mg) as an off-white solid.

mp. 102.5-104°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.75(4H, brs), 4.82(2H, s), 6.46(2H, d, J=8.5Hz), 6.69(1H, s), 6.83(2H, d, J=8.5Hz), 12.07(1H, brs).

MS: 262(M+H)$^+$

Step 7

Compound A

To a suspension of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (26 g) in ethanol (500 ml) was added 4N hydrogen chloride in ethyl acetate (25 ml) and cyanamide (6.3 g). The mixture was refluxed for 26 hours. The reaction mixture was cooled to ambient temperature and poured into a mixture of ethyl acetate (500 ml) and saturated sodium hydrogen carbonate solution (500 ml). The resulted precipitate was collected by filtration and washed with water (300 ml) and ethanol (300 ml) to give N-{4-[2-(4-{[amino(imino)methyl]-amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (18 g) as white crystals.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3H, s), 2.85(4H, s), 6.79(1H, s), 6.83(2H, d, J=7Hz), 7.10(2H, d, J=7Hz).

MS: 304(M+H)$^+$

Production Example 2: Synthesis of N-(4-(2-(4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl)ethyl)-1,3-thiazol-2-yl)acetamide

N-(4-(2-(4-Aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (1.8 g) prepared in a similar manner according to Step 6 of Production Example 1, 2-(methylsulfanyl)-4,5-dihydro-1,3-thiazole (918 mg), hydrochloric acid concentrate (0.57 ml) and 2-methoxyethanol (28 ml) were combined under nitrogen atmosphere, and stirred at 120°C for 10 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran / water, and made basic with aqueous potassium carbonate. The mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified by flash

column chromatography over silica gel with chloroform / methanol (30:1 → 20:1) as an eluent, and triturated with ethyl acetate to give N-(4-(2-(4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl)ethyl)-1,3-thiazol-2-yl)acetamide (484.7 mg) as an off-white solid.

mp. 218-219.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.84(4H, s), 3.26(2H, t, J=7.5Hz), 3.35(2H, t, J=7.5Hz), 4.02(1H, brs), 6.71(1H, brs), 7.05(2H, d, J=8.5Hz), 7.51(1H, brs), 9.25(1H, brs), 12.10(1H, brs).

MS: 347$(M+H)^+$

Production Example 3: Synthesis of N-(4-{(E)-2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethenyl}-1,3-thiazol-2-yl)acetamide

Step 1

A mixture of 4-nitrobenzyl bromide (6.35 g), triphenylphosphine (7.71 g) and N,N-dimethylformamide (50 ml) was stirred for 5 hours at room temperature. To the mixture were added potassium butoxide (3.96 g), and then N-(4-formyl-1,3-thiazol-2-yl)acetamide (5.0 g) prepared in a similar manner according to Step 4 of Production Example 1, and the mixture was stirred for 13 hours at the same temperature. The reaction mixture was poured into ethyl acetate (200 ml) and water (200 ml). The organic layer was washed with water (20 ml), dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected and washed with 30% ethyl acetate / diisopropyl ether to give N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (7.8 g).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 7.29(1H, d, J=16Hz), 7.48(1H, d, J=16Hz), 7.88(2H, d, J=7Hz), 8.22(2H, d, J=7Hz).

MS (M+H)=290

Step 2

A mixture of N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-

thiazol-2-yl}acetamide (250 mg), palladium on carbon (25 mg) and methanol (2.5 ml) was stirred under hydrogen atmosphere for 2 hours at ambient temperature. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The crystalline residue was collected and washed with isopropyl ether to give N-{4-[(E)-2-(4-aminophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (160 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.14(3H, s), 5.33(2H, s), 6.55(2H, d, J=7Hz), 6.82(1H, d, J=10Hz), 6.44(1H, s), 7.09(1H, d, J=10Hz), 7.20(2H, d, J=7Hz).

MS: 260(M+H)$^+$

Step 3

A mixture of N-{4-[(E)-2-(4-aminophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (200 mg), 2-(methylsulfanyl)-4,5-dihydro-1,3-thiazole (103 mg), hydrochrolic acid (0.064 ml) and 2-methoxyethanol (2 ml) was stirred at 120°C for 8 hours. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica-gel flash column chromatography with hexane:ethyl acetate (3:1) as an eluent. The crystalline residue was collected and washed with ethyl acetate to give N-(4-{(E)-2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethenyl}-1,3-thiazol-2-yl)acetamide (150 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.27(3H, s), 3.33-3.40(2H, m), 3.57-3.65(2H, m), 6.94(1H, s), 7.05(1H, d, J=12Hz), 7.29(1H, d, J=12Hz), 7.30(2H, d, J=7Hz), 7.57(2H, d, J=7Hz).

MS: 345(M+H)$^+$

Production Example 4: Synthesis of methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydriodide

Step 1

To an ice-cold solution of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (300 mg) prepared in a similar manner according to Step 6 of Production Example 1 in acetone

(5 ml) was added benzoyl isothiocyanate (187 mg) and the mixture was refluxed for 2 hours. The reaction mixture was cooled to 0°C. The precipitated crystals were filtered and washed with ice-cold acetone to give N-{4-[2-(4-{[(benzoylamino)carbonothioyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (359 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.25(3H, s), 2.90-3.05(4H, m), 6.51(1H, s), 7.21(2H, d, J=7Hz), 7.50-7.70(5H, m), 7.89(2H, d, J=7Hz), 9.03(1H, s), 9.12(1H, s).

MS (M+H)=425

Step 2

A mixture of N-{4-[2-(4-{[(benzoylamino)carbonothioyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (200 mg), 6N aqueous sodium hydroxide (0.19 ml) and ethanol (2 ml) was stirred at 60°C for 2 hours. The reaction mixture was cooled to ambient temperature and neutralized with 1N hydrochloric acid (1.2 ml). The precipitated crystals were filtered and washed with water to give N-[4-(2-{4-[(aminocarbonothioyl)amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (120 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.88(4H, s), 6.75(1H, s), 7.15(2H, d, J=7Hz), 7.27(2H, d, J=7Hz), 9.60(1H, s).

MS (M+H)=321

Step 3

A mixture of N-[4-(2-{4-[(aminocarbonothioyl)amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (100 mg), methyl iodide (0.023 ml) and methanol (2 ml) was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and stirred for 30 minutes. The precipitated crystals were filtered and washed with ethyl acetate to give methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydriodide (130 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.13(3H, s), 2.68(3H, s), 2.87-

3.05(4H, m), 6.75(1H, s), 7.24(2H, d, J=7Hz), 7.35(2H, d, J=7Hz).

MS (M+H)=463

Production Example 5: Synthesis of N-(4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

A mixture of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (65 mg) prepared in a similar manner according to Step 6 of Production Example 1, ethyl 2-(methylsulfanyl)-4,5-dihydro-1H-imidazole-1-carboxylate (56 mg), acetic acid (0.1 ml), ethanol (0.9 ml) was stirred at 65°C for 6 hours, and then refluxed for 5 hours. The reaction mixture was poured into ethyl acetate (5 ml) and saturated aqueous sodium bicarbonate. The precipitated solid was filtered, and the solid was dissolved in 50% methanol/chloroform. The insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The solid residue was collected and washed with ethyl acetate to give N-(4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]-ethyl}-1,3-thiazol-2-yl)acetamide (40 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.72(4H, s), 3.33(4H, s), 6.73(1H, s), 6.85-7.08(4H, m).

MS (M+H)=330

Production Example 6: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}-2-methylpropanamide

Step 1

To an ice-cold mixture of ethyl 2-amino-1,3-thiazole-4-carboxylate (2 g) prepared in a similar manner according to Step 1 of the following Production Example 7, pyridine (1.3 ml) and dichloromethane (20 ml) was added isobutyryl chloride (0.91 ml) and stirred for 30 minutes. To the mixture was added saturated aqueous hydrogen bicarbonate (30 ml), and the organic layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected

and washed with ethyl acetate to give ethyl 2-(isobutyrylamino)-1,3-thiazole-4-carboxylate (1.34 g).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.30(6H, d, J=7Hz), 1.40(3H, t, J=7Hz), 2.57-2.73(1H, m), 4.41(2H, q, J=7Hz), 7.83(1H, s), 8.98(1H, s).

MS: 243$(M+H)^+$

Step 2

To a mixture of ethyl 2-(isobutyrylamino)-1,3-thiazole-4-carboxylate (1.4 g) and tetrahydrofuran (28 ml) was added lithium borohydride (252 mg) portionwise, and the mixture was refluxed for 6 hours. The reaction mixture was cooled to 0°C, quenched with methanol (5 ml) and concentrated *in vacuo*. The residue was suspended with 10% methanol / chloroform (100 ml), and the insoluble materials were filtered off. The filtrate was purified by flash column chromatography on silica-gel with 5% methanol / chloroform as an eluent. The crystalline residue was collected and washed with diisopropyl ether to give N-[4-(hydroxymethyl)-1,3-thiazol-2-yl]-2-methylpropanamide (1.0 g).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.32(6H, d, J=5Hz), 2.58-2.73(1H, m), 4.68(2H, s), 6.82(1H, s).

MS (M+H)=200

Step 3

A mixture of N-[4-(hydroxymethyl)-1,3-thiazol-2-yl]-2-methylpropanamide (520 mg), manganese (IV) oxide (2.26 g), methanol (0.5 ml) and chloroform (5 ml) was stirred at ambient temperature for 18 hours. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo*. The crystalline residue was collected and washed with diisopropyl ether to give N-(4-formyl-1,3-thiazol-2-yl)-2-methylpropanamide (365 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.13(6H, d, J=5Hz), 2.60-2.77(1H, m), 7.86(1H, s).

MS (M+H)=199

Step 4

A mixture of 4-nitrobenzyl bromide (381 mg), triphenylphosphine (463 mg) and N,N-dimethylformamide (3 ml) was stirred for 5 hours at room temperature. To the mixture were added potassium butoxide (238 mg) and then N-(4-formyl-1,3-thiazol-2-yl)-2-methylpropanamide (350 mg), and the mixture was stirred for 13 hours at the same temperature. The reaction mixture was poured into ethyl acetate (20 ml) and water (20 ml). The organic layer was washed with water (20 ml), dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected and washed to give 2-methyl-N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}propanamide (360 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.25(6x2/3H, d, J=5Hz), 1.30(6x1/3H, d, J=5Hz), 2.50-5.70(1H, m), 6.63(1H, s), 6.79(1x2/3H, s), 6.97(1x2/3H, s), 7.14(1x1/3H, d, J=12Hz), 7.33(1x1/3H, d, J=12Hz), 7.53(2x2/3H, d, J=7Hz), 7.62(2x1/3H, d, J=7Hz), 8.13(2x2/3H, d, J=7Hz), 8.22(2x1/3H, d, J=7Hz).

MS (M+H)=318

Step 5

A mixture of 2-methyl-N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}propanamide (333 mg), palladium on carbon (33 mg), acetic acid (1 ml), methanol (2 ml) and tetrahydrofuran (2 ml) was stirred under hydrogen atmosphere (4 atm) at ambient temperature for 5 hours. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with 5% methanol / ethyl acetate as an eluent. The solid residue was collected and washed with diisopropyl ether to give N-{4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-yl}-2-methylpropanamide (260 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.38(6H, d, J=5Hz), 2.57-2.73(1H, m), 2.39-2.43(4H, m), 6.45(1H, s), 6.62(2H, d, J=7Hz), 6.97(2H, d,

J=7Hz).

MS (M+H)=290

Step 6

The title compound was prepared in a similar manner according to Step 7 of Production Example 1.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.01(6H, d, J=5Hz), 2.62-2.78(1H, m), 2.83(4H, s), 6.72(2H, d, J=7Hz), 6.75(1H, s), 7.04(2H, d, J=7Hz).

MS (M+H)=332

Production Example 7: Synthesis of 2-(acetylamino)-N-(4-{[amino(imino)methyl]amino}phenyl)-1,3-thiazole-4-carboxamide

Step 1

A mixture of ethyl 3-bromo-2-oxopropanoate (100 g), thiourea (39 g) and ethanol (500 ml) was refluxed for 2 hours. The reaction mixture was concentrated *in vacuo*. The crystalline residue was collected and washed with ethyl acetate to give ethyl 2-amino-1,3-thiazole-4-carboxylate hydrobromide (116 g).

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.28(3H, t, J=7Hz), 4.26(2H, q, J=7Hz), 7.60(1H, s).

Step 2

To an ice-cold mixture of ethyl 2-amino-1,3-thiazole-4-carboxylate hydrobromide (80 g), pyridine (52.5 g) and dichloromethane (800 ml) was added acetyl chloride (27.3 g) dropwise at 0°C, and the mixture was stirred for 30 minutes at the same temperature. The reaction mixture was washed with water (500 ml), dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected and washed with ethyl acetate to give ethyl 2-(acetylamino)-1,3-thiazole-4-carboxylate (60 g).

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.29(3H, t, J=7Hz), 2.15(3H, s), 4.27(2H, q, J=7Hz), 8.03(1H, s).

MS (M+H)=215

Step 3

A mixture of ethyl 2-(acetylamino)-1,3-thiazole-4-carboxylate (2 g), 2N sodium hydroxide (7 ml) and methanol (13 ml) was stirred at ambient temperature for 5 hours. The reaction mixture was neutralized by 1N hydrochloric acid (14 ml). The precipitated crystals were filtered and washed with water to give 2-(acetylamino)-1,3-thiazole-4-carboxylic acid (1.3 g).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.14(3H, s), 7.94(1H, s).

Step 4

A mixture of 2-(acetylamino)-1,3-thiazole-4-carboxylic acid (500 mg), tert-butyl 4-aminophenylcarbamate (615 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (566 mg), 1-hydroxybenzotriazole (399 mg) and dichloromethane (5 ml) was stirred at ambient temperature for 3 hours. The reaction mixture was washed with saturated aqueous sodium hydrogen bicarbonate, and the organic layer was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with 3% methanol / chloroform as an eluent. The crystalline residue was collected and washed with ethyl acetate to give tert-butyl 4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}amino)phenylcarbamate (580 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.48(9H, s), 2.18(3H, s), 7.42(2H, d, J=7Hz), 7.61(2H, d, J=7Hz), 7.91(1H, s), 9.32(1H, s), 9.63(1H, s).

MS (M+H)=377

Step 5

To a solution of tert-butyl 4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}amino)phenylcarbamate (85 mg) in methanol (1 ml) was added 4N hydrogen chloride in ethyl acetate (1 ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The solid residue was collected and washed with

ethyl acetate to give 2-(acetylamino)-N-(4-aminophenyl)-1,3-thiazole-4-carboxamide hydrochloride (70 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 7.42(2H, d, J=7Hz), 7.37(2H, d, J=7Hz), 7.41(1H, s).

MS (M+H)=313

Step 6

A mixture of 2-(acetylamino)-N-(4-aminophenyl)-1,3-thiazole-4-carboxamide hydrochloride (70 mg), cyanamide (11 mg) and 2-methoxyethanol (2 ml) was stirred at 100°C for 72 hours. The reaction mixture was concentrated *in vacuo*. To the residue was added ethyl acetate (5 ml) and saturated aqueous sodium hydrogen bicarbonate (5 ml). The precipitated solid was filtered and washed with ethyl acetate and water to give 2-(acetylamino)-N-(4-{[amino(imino)methyl]amino}phenyl)-1,3-thiazole-4-carboxamide (45 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 7.60-7.88(4H, br), 7.95(1H, s).

MS (M+H)=319

Production Example 8: Synthesis of N-(4-{2-[4-(ethanimidoylamino)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

N-(4-(2-(4-Aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (100 mg) prepared in a similar manner according to Step 6 of Production Example 1, methyl ethanimidothioate hydriodide (166 mg) and methanol (3 ml) were combined, and refluxed for 1.5 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography over NH silica gel with chloroform / methanol (20:1 → 10:1) as an eluent to give N-(4-{2-[4-(ethanimidoylamino)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (165 mg) as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.03(3H, brs), 2.19(3H, s), 2.92(4H, s), 6.47(1H, s), 6.78(2H, d, J=8.0Hz), 7.08(2H, d, J=8.0Hz).

MS: 303$(M+H)^+$

Production Example 9: Synthesis of N-[4-(2-{4-[amino(imino)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide hydrochloride

Step 1

4-(Bromomethyl)benzonitrile (1.73 g), triphenylphosphine (2.31 g) and N,N-dimethylformamide (20 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 hours. Then potassium tert-butoxide (1.19 g) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (1.5 g) prepared in a similar manner according to Step 4 of Production Example 1 were added to the mixture, and stirred at room temperature for 3 hours. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with 1N-hydrochloric acid, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:1) as an eluent, and triturated with ethyl ether to give a mixture of N-{4-[(Z)-2-(4-cyanophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide and N-{4-[(E)-2-(4-cyanophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (Z : E = 3 : 1) (1.63 g) as a pale yellow solid.

mp. 175-176°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.13(3Hx3/4, s), 2.16(3Hx1/4, s), 6.59(1Hx3/4, d, J=13.0Hz), 6.65(1Hx3/4, d, J=13.0Hz), 7.11(1Hx3/4, s), 7.24(1Hx1/4, d, J=16.0Hz), 7.28(1Hx1/4, s), 7.40(1Hx1/4, d, J=16.0Hz), 7.65(2Hx3/4, d, J=8.5Hz), 7.74(2Hx1/4, d, J=8.5Hz), 7.75(2Hx3/4, d, J=8.5Hz), 7.83(2Hx1/4, d, J=8.5Hz), 12.00(1H, brs).

MS: 270$(M+H)^+$

Step 2

A mixture of N-{4-[(Z)-2-(4-cyanophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide and N-{4-[(E)-2-(4-

cyanophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (Z : E = 3 : 1) (1.5 g), 10% palladium on carbon (323 mg), methanol (20 ml), tetrahydrofuran (10 ml) and acetic acid (5 ml) were combined. The reaction mixture was stirred under 4 atm hydrogen at ambient temperature for 9 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:1) → chloroform / methanol (30:1) as an eluent, and triturated with ethyl ether to give N-{4-[2-(4-cyanophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (1.18 g) as a colorless solid.

mp. 205-206.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.90(2H, t, J=8.0Hz), 3.01(2H, t, J=8.0Hz), 6.73(1H, s), 7.40(2H, d, J=8.0Hz), 7.74(2H, d, J=8.0Hz), 12.09(1H, brs).

MS: 272$(M+H)^+$

Step 3

N-{4-[2-(4-Cyanophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (600 mg) was dissolved in ethanol (5 ml) and chloroform (5 ml), and then hydrochloric acid gas was bubbled at 0°C for 5 minutes with stirring. The reaction mixture was stood for 15 hours, and concentrated *in vacuo*. The residual solid was washed with diethyl ether to give ethyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzenecarboximidoate hydrochloride (924.7 mg) as a pale green solid.

mp. 129-130°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.48(3H, t, J=7.0Hz), 2.12(3H, s), 2.95(2H, t, J=8.0Hz), 3.07(2H, t, J=8.0Hz), 4.61(2H, q, J=7.0Hz), 6.72(1H, s), 7.46(2H, d, J=8.5Hz), 8.02(2H, d, J=8.5Hz), 11.25(1H, brs), 11.98(1H, brs), 12.11(1H, brs).

MS: 318$(M+H)^+$ free

Step 4

Ethyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-

yl]ethyl}benzenecarboximidoate hydrochloride (300 mg) was dissolved in ethanol (6 ml). Then ammonium chloride (68 mg) and ammonia in methanol (1 ml) were added to the solution. The reaction mixture was refluxed for 5 hours under nitrogen atmosphere. After cooled to room temperature, the suspension was filtered *in vacuo*. The filtrate was concentrated *in vacuo*, and the residue was solidified with ethanol / diethyl ether to give N-[4-(2-{4-[amino(imino)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide hydrochloride (234 mg) as a colorless solid.

mp. 229.5-231°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.94(2H, t, J=8.0Hz), 3.06(2H, t, J=8.0Hz), 6.75(1H, s), 7.44(2H, d, J=8.5Hz), 7.76(2H, d, J=8.5Hz), 12.10(1H, brs).

MS: 289$(M+H)^+$ free

Production Example 10: Synthesis of N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)-2-{[amino(imino)methyl]amino}-acetamide hydrochloride

Step 1

A mixture of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (100 mg) prepared in a similar manner according to Step 6 of Production Example 1, ((tert-butoxycarbonyl)amino)acetic acid (74 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (81 mg), 1-hydroxybenzotriazole (57 mg) and dichloromethane (5 ml) was stirred at ambient temperature for 3 hours. The reaction mixture was washed with saturated aqueous sodium hydrogen bicarbonate, and the organic layer was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica-gel with 3% methanol / chloroform as an eluent. The crystalline residue was collected and washed with ethyl acetate to give tert-butyl 2-[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]-2-oxoethylcarbamate (580 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.47(9H, s), 2.25(3H, s), 2.92(4H, s),

3.92(2H, d, J=5Hz), 6.46(1H, s), 7.10(2H, d, J=7Hz), 7.38(2H, d, J=7Hz).

MS (M+H)=419

Step 2

To a solution of tert-butyl 2-[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]-2-oxoethylcarbamate (100 mg) in ethyl acetate (1 ml) was added 4N hydrogen chloride in ethyl acetate (1 ml), and the mixture was stirred at ambient temperature for 103 hours. The precipitated solid was filtered and washed with ethyl acetate to give N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)-2-aminoacetamide hydrochloride (80 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.87(4H, s), 6.70(1H, s), 7.17(2H, d, J=7Hz), 7.49(2H, d, J=7Hz).

MS (M+H)=319

Step 3

The title compound was prepared in a similar manner according to Step 7 of Production Example 1.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.80-2.95(4H, m), 3.76(2H, s), 6.70(1H, s), 7.26(2H, d, J=7Hz), 7.49(2H, d, J=7Hz), 8.16(2H, s).

MS (M+H)=361

Production Example 11: Synthesis of N-{4-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

Aluminium chloride (1.63 g) was dissolved in 1,2-dichloroethane (15 mL). Chloroacetylchloride (0.732 mL) was added to the mixture at 0°C, and stirred additionally for 20 minutes, then N-(2-phenylethyl)acetamide (1 g) in 1,2-dichloroethane (5 mL) was added dropwise. The mixture was stirred for 1 hour at room temperature, and then poured into ice-water. The mixture was extracted with

chloroform, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated *in vacuo*. The solid was washed with ethyl acetate and ethyl ether, and dried *in vacuo* to give N-{2-[4-(2-chloroacetyl)phenyl]ethyl}-acetamide as a white powder (1.18 g, 80.4%).

^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm): 7.92(2H, d, J=6Hz), 7.34(2H, d, J=6Hz), 5.66(1H, br), 4.70(2H, s), 3.55-3.60(2H, m), 2.90-2.94(2H, m), 1.98(3H, s).

Step 2

N-{2-[4-(2-Chloroacetyl)phenyl]ethyl}acetamide (1.06 g) and thiourea (505 mg) were dissolved in ethanol (20 mL). The mixture was refluxed for 1 hour and allowed to cool to room temperature. The white solid was collected with filtration and washed with ethanol to give N-{2-[4-(2-amino-1,3-thiazol-4-yl)phenyl]ethyl}acetamide hydrochloride (1.19 g, 90.4%).

MS m/z 262 (M++1).

^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm): 7.93-7.96(2H, m), 7.69(2H, d, J=6Hz), 7.30(2H, d, J=6Hz), 7.16(1H, s), 3.23-3.30(2H, m), 2.70-2.76(2H, m), 1.78 (3H, s).

Step 3

N-{2-[4-(2-Amino-1,3-thiazol-4-yl)phenyl]ethyl}acetamide (0.6 g) was dissolved in ethanol (10 mL) and hydrochloric acid concentrate (10 mL). The mixture was refluxed for 5 hours. The solvent was evaporated *in vacuo*. The residue was washed with ethyl ether to give 4-[4-(2-aminoethyl)phenyl]-1,3-thiazol-2-amine dihydrochrolide (0.5 g, 84.6%).

MS m/z 220 (M++1).

^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm): 8.15(3H, br), 7.78(2H, d, J=6Hz), 7.39(2H, d, J=6Hz), 7.24(1H, s), 3.03-3.10(2H, m), 2.90-2.98(2H, m).

Step 4

4-[4-(2-Aminoethyl)phenyl]-1,3-thiazol-2-amine dihydrochrolide (0.45 g) was dissolved in 1,4-dioxane (10 mL),

water (3 mL) and 1N sodium hydroxide solution (3.1 mL). Di-tert-butyl dicarbonate (336 mg) was added at 0°C. The mixture was stirred at room temperature overnight, then extracted with ethyl acetate, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated *in vacuo*. The solid was washed with ethyl ether, and dried *in vacuo* to give tert-butyl {2-[4-(2-amino-1,3-thiazol-4-yl)phenyl]ethyl}-carbamate as a white solid (311 mg, 63.2%).

MS m/z 320 (M++1).

^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm): 7.69(2H, d, J=6Hz), 7.18(2H, d, J=6Hz), 7.02(2H, br), 7.69(1H, s), 3.10-3.27(2H, m), 2.65-2.72(2H, m), 1.37(9H, s).

Step 5

tert-Butyl {2-[4-(2-amino-1,3-thiazol-4-yl)phenyl]ethyl}carbamate (290 mg) was dissolved in dichloromethane (5 mL), then acetic anhydride (0.103 mL), 4-dimethylaminopyridine (10 mg) and pyridine (0.147 mL) were added. The mixture was stirred overnight. The mixture was extracted with chloroform, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated *in vacuo*. The solid was washed with ethyl ether, and dried *in vacuo* to give tert-butyl (2-{4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)carbamate as a white solid (280 mg, 85.3%).

MS m/z 362 (M++1).

^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm): 7.80(2H, d, J=6Hz), 7.53(1H, s), 7.24(2H, d, J=6Hz), 6.90(1H, m), 3.12-3.18(2H, m), 2.16-2.63(2H, m), 2.16(3H, s), 1.37(9H, s).

Step 6

tert-Butyl (2-{4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)carbamate (250 mg) was dissolved in ethyl acetate (4 mL) and 4 N hydrogen chloride in ethyl acetate (2 mL). The solvent was evaporated *in vacuo*. The solid was

washed with ethyl acetate and ethyl ether to give N-{4-[4-(2-aminoethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride (220 mg, 106%).

MS m/z 262 (M++1).

^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm): 8.05(3H, br), 7.85(2H, d, J=6Hz), 7.58(1H, s), 7.32(2H, d, J=6Hz), 3.12-3.18(2H, m), 2.88-2.94(2H, m), 2.16(3H, s).

Step 7

N-{4-[4-(2-Aminoethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride (200 mg) and diisopropylethylamine (0.175 mL) were dissolved in tetrahydrofuran (5 mL). The mixture was stirred at room temperature overnight, then evaporated *in vacuo*. The residue was purified with silica gel chromatography (5% methanol / chloroform) to give di-tert-butyl {[(2-{4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)amino]methylidene}-biscarbamate (268 mg, 79.2%).

MS m/z 504 (M++1).

Step 8

Di-tert-butyl {[(2-{4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)amino]methylidene}biscarbamate (268 mg, 79.2%) (170 mg) was dissolved in 4 N hydrogen chloride in 1,4-dioxane (5 mL). The mixture was stirred at room temperature for 2 days, and then evaporated *in vacuo*. The residue was washed with ethyl ether, dried *in vacuo* to give N-{4-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride (50 mg, 43.6%).

MS m/z 304 (M++1).

^{1}H-NMR (300 MHz, DMSO-d_6), δ (ppm): 7.83(2H, d, J=8Hz), 7.62-7.66(1H, m), 7.56(1H, s), 7.34(2H, d, J=8Hz), 3.37-3.45(2H, m), 2.78-2.85(2H, m), 2.16(3H, s).

Production Example 12: Synthesis of N-(4-{2-[4-(aminomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

Step 1

To a mixture of N-(4-{2-[4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (50 mg) prepared in a similar manner according to Step 3 of the following Production Example 16, carbon tetrabromide (72 mg) and dichloromethane (1 ml) was added triphenylphosphine (71 mg), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was purified by flash column chromatography on silica gel with 1% methanol / chloroform as an eluent. The crystalline residue was collected and washed with diisopropyl ether to give N-(4-{2-[4-(bromomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (48 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.25(3H, s), 2.85-3.03(4H, m), 4.49(2H, s), 6.48(1H, s), 7.13(2H, d, J=7Hz), 7.30(2H, d, J=7Hz).

MS (M+H)=339

Step 2

To a mixture of N-(4-{2-[4-(bromomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (100 mg), tetrahydrofuran (2 ml) and N,N-dimethylformamide (2 ml) was added sodium diformylimide (42 mg), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was diluted with water (3 ml), and the precipitated solid was filtered and washed with water to give N-[4-(2-{4-[(diformylamino)-methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (80 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.23(3H, s), 2.83-3.00(4H, m), 4.72(2H, s), 6.48(1H, s), 7.10(2H, d, J=7Hz), 7.38(2H, d, J=7Hz).

MS (M+H)=318

Step 3

To a solution of N-[4-(2-{4-[(diformylamino)methyl]-phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (56 mg) in methanol (0.5 ml) was added 4N hydrogen chloride in ethyl acetate (0.5

ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The residue was separated between chloroform (5 ml) and saturated aqueous sodium hydrogen bicarbonate (5 ml), and the aqueous layer was extracted with chloroform (5 ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give N-(4-{2-[4-(aminomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (50 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.80-3.00(4H, m), 3.92-4.05(2H, m), 6.72(1H, s), 7.24(2H, d, J=7Hz), 7.37(2H, d, J=7Hz).

MS (M+H)=276

Production Example 13: Synthesis of ethyl 4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-ylcarbamate hydrochloride

Step 1: ethyl 4-(hydroxymethyl)-1,3-thiazol-2-ylcarbamate

A mixed solution of ethyl 4-(chloromethyl)-1,3-thiazol-2-ylcarbamate (500 mg) in 1,4-dioxane (5 ml) and water (10 ml) was refluxed with stirring for 3.5 hours. After cooling, it was concentrated under reduced pressure. The mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of hexane and ethyl acetate (2:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give colorless syrup (450 mg, 98.2%).

MS (ES+); 203 $(M+H)^+$

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.39(3H, t, J=7.0Hz), 4.39(2H, q, J=7.0Hz), 4.61(2H, s), 6.80(1H, s).

Step 2: ethyl 4-formyl-1,3-thiazol-2-ylcarbamate

To a mixed solution of ethyl 4-(hydroxymethyl)-1,3-

thiazol-2-ylcarbamate (446 mg) in chloroform (30 ml) and methanol (3 ml) was added portionwise manganese (IV) oxide chemicals treated (1.92 g) at room temperature. After the mixture was stirred at the same temperature for 2 hours, then treated manganese (IV) oxide chemicals (250 mg) was added again to the solution, and it was stirred at 50°C for 3 hours. Manganese (IV) oxide was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give colorless powder (470 mg, 106.4%).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.36(3H, t, J=7.0Hz), 4.34(2H, q, J=7.0Hz), 7.83(1H, s), 9.54(1H, br), 9.88(1H, s).

Step 3

Ethyl 4-[2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-ylcarbamate (E-Z mixture) was obtained in a similar manner according to Step 5 of Production Example 1.

^{1}H-NMR ($CDCl_3$) (cis-trans product mixture), δ (ppm): 1.20-1.40(3H, m), 4.20-4.40(2H, m), 6.60, 6.66(1.2H, ABq, J=13Hz), 6.74(0.6H, s), 6.94(0.4H, s), 7.12, 7.30(0.8H, ABq, J=16Hz), 7.53(1.2H, d, J=8.9Hz), 7.61(0.8H, d, J=8.9Hz), 8.11(1.2H, d, J=8.9Hz), 8.22(0.8H, d, J=8.9Hz).

Step 4

Ethyl 4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-ylcarbamate was obtained in a similar manner according to Step 6 of Production Example 1.

MS (ES+); 292$(M+H)^+$

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.24(3H, t, J=7.1Hz), 2.65-2.80(4H, m), 4.18(2H, q, J=7.1Hz), 4.82(2H, br), 6.46(2H, d, J=8.5Hz), 6.69(1H, s), 6.84(2H, d, J=8.5Hz).

Step 5

Ethyl 4-[2-(4-{N',N"-bis(tert-butoxycarbonyl)-[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-ylcarbamate was obtained in a similar manner according to Step 3 of the following Production Example 14.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.29(3H, t, J=7.0Hz), 1.40-1.70(18H, m), 2.94(4H, s), 4.27(2H, q, J=7.0Hz), 6.45(1H, s), 7.12(2H, d, J=8.4Hz), 7.48(2H, d, J=8.4Hz), 10.25(1H, s).

Step 6

The title compound was prepared in a similar manner according to Step 5 of the following Production Example 14.

MS (ES+); 334 $(M+H)^+$ free

^{1}H-NMR ($DMSO-d_6$), δ (ppm): 1.24(3H, t, J=7.0Hz), 2.80-3.00(4H, m), 4.19(2H, q, J=7.0Hz), 6.76(1H, s), 7.14(2H, d, J=8.4Hz), 7.28(2H, d, J=8.4Hz), 7.46(3H, br), 9.91(1H, s).

Production Example 14: Synthesis of N-{4-[2-(3-{[amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1: N-{4-[2-(3-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (E-Z mixture)

To a solution of 1-(bromomethyl)-3-nitrobenzene (276 mg) in N,N-dimethylformamide (7 mL) was added triphenylphosphine (335 mg) at room temperature. After the mixed solution was stirred for 4 hours, potassium tert-butoxide (172 mg) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (217 mg) were successively added to the solution at the same temperature. After the whole solution was stirred at room temperature for 5 hours, the mixture was poured into water, the pH of the aqueous layer was adjusted to 7 with 1N-hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of n-hexane and ethyl acetate (4:1). The

fractions containing the objective compound were collected and evaporated under reduced pressure to give brown powder of the title compound (E-Z mixture) (323 mg, 87.4%).

^{1}H-NMR (DMSO-d_6) (cis-trans product mixture), δ (ppm): 2.11(2.49H, s), 2.16(0.51H, s), 6.66(1.66H, s), 7.13(0.83H, s), 7.28(0.17H, s), 7.29, 7.46(0.34H, ABq, J=16Hz), 7.60(1H, t, J=7.9Hz), 7.91(0.83H, d, J=7.9Hz), 8.01(0.17H, d, J=7.9Hz), 8.09-8.13(1H, m), 8.28(0.83H, m), 8.38(0.17H, m).

Step 2: N-{4-[2-(3-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide

N-{4-[2-(3-Nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (E,Z mixture) (315 mg) in a mixed solvent of methyl alcohol (3 ml), tetrahydrofuran (6 ml), and acetic acid (1 ml) was hydrogenated over 10% Palladium on carbon (50% wet, 200 mg) under 4.3 atmospheric pressure at room temperature for 3 hours. The catalyst was removed off by filtration, and the filtrate was evaporated *in vacuo*. The residue was poured into water, the pH of the aqueous layer was adjusted to 9 with aqueous sodium hydrogen carbonate. The resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (9 g) using a mixed solvent of n-hexane and ethyl acetate (2:1 to 1:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give syrup. The syrup of the objective compound was changed to solid in freezer (275 mg, 96.6%).

MS (ES+); 262 $(M+H)^+$

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.23(3H, s), 2.80-3.00(4H, m), 3.60(2H, br), 6.51(1H, s), 6.45-6.65(3H, m), 7.06(1H, t, J=7.9Hz), 9.45(1H, br).

Step 3: N-{4-[2-(3-{[N',N"-bis(tert-butoxycarbonyl)amino-

(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

To a solution of N-{4-[2-(3-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (267 mg) in tetrahydrofuran (3 ml) was added N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (317 mg) at room temperature. After the mixed solution was stirred for 3 days at the same temperature, and then evaporated under reduced pressure, the resulting residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of n-hexane and ethyl acetate (4:1 to 3:2). The fractions containing the objective compound were collected and evaporated under reduced pressure to give colorless foam of the title compound (316 mg, 61.4%).

MS (ES+); 504 $(M+H)^+$

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.40-1.80(18H, m), 2.25(3H, s), 2.97(4H, m), 6.37(1H, m), 6.53(1H, s), 6.91(1H, d, J=7.9Hz), 7.23(1H, t, J=7.9Hz), 7.34(1H, s), 7.52(1H, d, J=7.9Hz), 7.63-7.64(1H, m), 10.28(1H, s).

Step 4: N-{4-[2-(3-{[N',N"-bis(tert-butoxycarbonyl)amino-(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide

To a suspension of N-{4-[2-(3-{[N',N"-bis(tert-butoxycarbonyl)amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (115 mg) in methanol (3 ml) was added N-bromosuccinimide (44.7 mg) at room temperature. After the mixed solution was stirred at the same temperature for 1 hour, the resulting precipitate was collected by filtration, washed with a mixed solvent of diisopropyl ether and n-hexane (1:1). The title compound was obtained as white powder (70 mg, 52.6%).

MS (ES+); 582 $(M+H)^+$

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.40-1.75(18H, m), 2.21(3H, s), 2.85-3.00(4H, m), 6.93(1H, d, J=7.9Hz), 7.23(1H, t, J=7.9Hz), 7.30(1H, s), 7.51(1H, d, J=7.9Hz), 9.26(1H, br), 10.26(1H,

br), 11.63(1H, br).

Step 5

To a solution of N-{4-[2-(3-{[N',N"-bis(tert-butoxycarbonyl)amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide (64 mg) in dichloromethane (0.5 ml) was added dropwise 4N-hydrogen chloride in 1,4-dioxane (2 ml) at room temperature. After being stirred at the same temperature for 20 hours, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in a minimum methanol, and the solution was gradually diluted with ethyl acetate. The resulting precipitate was collected by filtration, washed with diisopropyl ether. The title compound was obtained as colorless powder (37 mg, 80.4%).

MS (ES+); 382 $(M+H)^+$ free

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.14(3H, s), 2.80-3.00(4H, m), 7.00-7.15(3H, m), 7.35(1H, t, J=7.9Hz), 7.51(4H, br), 10.01(1H, br), 12.42(1H, br).

Production Example 15: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1-a

Di-tert-butyl {[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 6 of Production Example 1 in a similar manner according to the following Step 5 of Production Example 18.

mp. 275.5-276°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.11(3H, s), 2.82-2.96(4H, m), 6.74(1H, s), 7.18(2H, d, J=8.5Hz), 7.42(2H, d, J=8.5Hz), 9.94(1H, brs), 11.44(1H, brs), 12.09(1H, brs).

MS: 504 $(M+H)^+$

Step 1-b

Di-tert-butyl {[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (310 mg) prepared in a similar manner according to Step 5 of the following Production Example 18 was dissolved in methanol (6 ml) and tetrahydrofuran (3 ml) under nitrogen atmosphere. Then N-bromosuccinimide (164 mg) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 4 hours, and concentrated *in vacuo*. Chloroform and saturated sodium hydrogen carbonate solution were added to the residue. The organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (2:1) as an eluent to give di-tert-butyl {[(4-{2-[2-(acetylamino)-5-bromo-1,3-thiazol-4-yl]ethyl}phenyl)amino]-methylidene}biscarbamate (271.4 mg) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.22(3H, s), 2.90(4H, s), 7.13(2H, d, J=8.0Hz), 7.45(2H, d, J=8.0Hz).

MS: 582$(M+H)^+$

Step 2

Di-tert-butyl {[(4-{2-[2-(acetylamino)-5-bromo-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (113 mg) and 4N hydrochloric acid in 1,4-dioxane solution (2 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo*. The residue was washed with ethyl acetate to give N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide hydrochloride (16.8 mg) as a pale yellow amorphous solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.14(3H, s), 2.82-2.97(4H, m), 7.14(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.40(3H, brs),

9.81(1H, brs), 12.41(1H, brs).

MS: 382$(M+H)^+$ free

Production Example 16: Synthesis of N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide

Step 1

[4-(Methoxycarbonyl)benzyl](triphenyl)phosphonium bromide (6.06 g) and N,N-dimethylformamide (50 ml) were combined under nitrogen atmosphere. Then potassium tert-butoxide (1.66 g) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (2.1 g) prepared in a similar manner according to Step 4 of Production Example 1 were added to the suspension at 0°C. The reaction mixture was stirred at room temperature for 6 hours, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with 1N-hydrochloric acid, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / methanol (20:1 → 10:1) as an eluent, and triturated with ethyl ether to give a mixture of methyl 4-{(Z)-2-[2-(acetylamino)-1,3-thiazol-4-yl]ethenyl}benzoate and methyl 4-{(E)-2-[2-(acetylamino)-1,3-thiazol-4-yl]ethenyl}benzoate (Z : E = 3 : 1) (4.05 g) as a colorless solid.

mp. 164-165.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.13(3Hx3/4, s), 2.16(3Hx1/4, s), 3.85(3H, s), 6.61(2Hx3/4, s), 7.05(1Hx3/4, s), 7.26(1Hx1/4, d, J=15.5Hz), 7.27(1Hx1/4, s), 7.37(1Hx1/4, d, J=15.5Hz), 7.64(2Hx3/4, d, J=8.5Hz), 7.69(2Hx1/4, d, J=8.5Hz), 7.90(2Hx3/4, d, J=8.5Hz), 7.94(2Hx1/4, d, J=8.5Hz), 12.05(1H, brs).

MS: 303$(M+H)^+$

Step 2

Methyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzoate was prepared in a similar manner according

to Step 2 of Production Example 9.

mp. 170-171°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.86-2.95(2H, m), 2.97-3.05(2H, m), 3.83(3H, s), 6.72(1H, s), 7.35(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 12.08(1H, brs).

MS: 305 $(M+H)^+$

Step 3

To a stirred solution of methyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzoate (1.8 g) in dry tetrahydrofuran (36 ml) was added dropwise 1.0 M diisobutylaluminium hydride solution in toluene (20.7 ml) at -78°C over 15 minutes under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 hours, and then the reaction was quenched with water (1 ml). The mixture was stirred at room temperature for 30 minutes, dried over anhydrous magnesium sulfate, and filtered through a pad of Celite. The solvent was evaporated *in vacuo*. The residual solid was washed with ethyl ether to give N-(4-{2-[4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (1.03 g) as a colorless solid.

mp. 162-165°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.80-2.95(4H, m), 4.44(2H, d, J=5.5Hz), 5.09(1H, t, J=5.5Hz), 6.72(1H, s), 7.14(2H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 12.08(1H, brs).

MS: 277 $(M+H)^+$

Step 4

N-(4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (250 mg), 2-hydroxy-1H-isoindole-1,3(2H)-dione (155 mg), triphenylphosphine (249 mg) and tetrahydrofuran (5 ml) were combined under nitrogen atmosphere, and then diethyl azodicarboxylate (0.15 ml) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 6 hours, poured into saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer

was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / methanol (20:1) as an eluent, and triturated with ethyl acetate to give N-{4-[2-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (218.2 mg) as a colorless solid.

mp. 225-226°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.82-3.00(4H, m), 5.12(2H, s), 6.69(1H, s), 7.23(2H, d, J=8.0Hz), 7.41(2H, d, J=8.0Hz), 7.86(4H, s), 12.08(1H, brs).

MS: 422(M+H)$^+$

Step 5

N-{4-[2-(4-{[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (200 mg), methylhydrazine (0.038 ml) and dichloromethane (4 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 hours, and filtered *in vacuo*. The filtrate was washed with saturated sodium hydrogen carbonate solution, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with acetonitrile to give N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (81.8 mg) as a colorless solid.

mp. 130-130.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.82-2.97(4H, m), 4.51(2H, s), 6.01(2H, s), 6.73(1H, s), 7.17(2H, d, J=8.0Hz), 7.22(2H, d, J=8.0Hz), 12.09(1H, brs).

MS: 292(M+H)$^+$

Production Example 17: Synthesis of N-{4-[2-(4-{[(methyleneamino)oxy]methyl}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

N-[4-(2-{4-[(Aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (30 mg) prepared in a similar manner according to Production Example 16, 37% formaldehyde (8 μl) and dry methanol (1 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 hours and concentrated *in vacuo*. The residue was purified by preparative silica gel column chromatography with chloroform / methanol (20:1) as an eluent, and triturated with ethyl ether to give N-{4-[2-(4-{[(methyleneamino)oxy]methyl}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (20.9 mg) as a colorless solid.

mp. 136.5-137°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.83-2.97(4H, m), 5.01(2H, s), 6.61(1H, d, J=7.5Hz), 6.73(1H, s), 7.09(1H, d, J=7.5Hz), 7.18(2H, d, J=8.0Hz), 7.24(2H, d, J=8.0Hz), 12.08(1H, brs).

MS: 304(M+H)$^+$

Production Example 18: Synthesis of N-{5-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

A solution of 1,1,3,3-tetramethoxypropane (10 g) and hydrochloric acid concentrate (0.43 ml) in water (11 ml) was stirred at room temperature for 10 minutes. Bromine (3.14 ml) was added dropwise to the solution at room temperature over 50 minutes. The reaction mixture was stirred at room temperature for 20 minutes, and concentrated *in vacuo*. The residual solid was washed with water to give 2-bromomalonaldehyde (3.6 g) as a yellow solid.

mp. 147-148°C

^{1}H-NMR ($CDCl_3$), δ (ppm): 4.73-4.80(1H, m), 8.47(2H, brs).

MS: 149(M-H)$^+$

Step 2

N'-((E)-Ethanoyl)carbamimidothioic acid (2.74 g) and

acetone (20 ml) were combined under nitrogen atmosphere. Then 2-bromomalonaldehyde (3.5 g) was added to the solution under reflux. The reaction mixture was refluxed for an hour, and cooled to room temperature. The precipitate was filtered *in vacuo*. The solid was washed with water and acetone, and purified by flash column chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give N-(5-formyl-1,3-thiazol-2-yl)acetamide (1.21 g) as an off-white solid.

mp. 235-235.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.21(3H, s), 8.41(1H, s), 9.95(1H, s), 12.71(1H, brs).

MS: 169$(M-H)^+$

Step 3

N-{5-[(Z)-2-(4-Nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 1.

mp. 221-223°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.07(3H, s), 6.63(1H, d, J=12.0Hz), 6.92(1H, d, J=12.0Hz), 7.55(1H, s), 7.62(2H, d, J=9.0Hz), 8.24(2H, d, J=9.0Hz), 12.16(1H, brs).

MS: 290$(M+H)^+$

Step 4

A mixture of N-{5-[(Z)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (1 g) and 10% palladium carbon (1.04 g) in ethyl acetate (100 ml) and N,N-dimethylformamide (20 ml) was stirred under 4 atm hydrogen at ambient temperature for 4 hours. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / methanol (30:1 → 20:1) as an eluent, and triturated with ethyl ether to give N-{5-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (240.9 mg) as an off-white solid.

mp. 218-219.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.70(2H, t, J=7.5Hz), 2.92(2H, t, J=7.5Hz), 4.85(2H, s), 6.47(2H, d, J=8.5Hz), 6.86(2H, d, J=8.5Hz), 7.08(1H, s), 11.86(1H, brs).

MS: 262(M+H)$^+$

Step 5

N-{5-[2-(4-Aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (100 mg), N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (119 mg), N,N-dimethylformamide (1 ml) and tetrahydrofuran (2 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at 50°C for 5.5 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by preparative silica gel column chromatography with n-hexane / ethyl acetate (1:2) as an eluent to give di-tert-butyl {[(4-{2-[2-(acetylamino)-1,3-thiazol-5-yl]ethyl}phenyl)amino]-methylidene}biscarbamate (93.9 mg) as a colorless solid.

mp. 203-205°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.40(9H, s), 1.51(9H, s), 2.10(3H, s), 2.87(2H, t, J=7.5Hz), 3.02(2H, t, J=7.5Hz), 7.11(1H, s), 7.21(2H, d, J=8.5Hz), 7.45(2H, d, J=8.5Hz), 9.96(1H, brs), 11.43(1H, brs), 11.88(1H, brs).

MS: 504(M+H)$^+$

Step 6

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 105-107°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.91(2H, t, J=7.5Hz), 3.04(2H, t, J=7.5Hz), 7.14(1H, s), 7.14(2H, d, J=8.5Hz), 7.32(2H, d, J=8.5Hz), 7.46(3H, brs), 9.89(1H, s), 11.95(1H, brs).

MS: 304(M+H)$^+$ free

Production Example 19: Synthesis of N-{4-[2-(4-

{[imino(methylamino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

A mixture of methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydriodide (50 mg) prepared in a similar manner according to Production Example 4, 40% methylamine in methanol (0.056 ml) and ethanol (1 ml) was stirred at ambient temperature for 20 hours. The precipitated crystals were filtered and washed with ethanol to give N-{4-[2-(4-{[imino(methylamino)methyl]amino}phenyl)-ethyl]-1,3-thiazol-2-yl}acetamide (18 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.64(3H, s), 2.83(4H, s), 6.67(2H, d, J=7Hz), 6.73(1H, s), 7.01(2H, d, J=7Hz).

MS (M+H)=318

Production Example 20: Synthesis of N-{4-[2-(4-{[amino(imino)-methyl]amino}phenyl)ethyl]-5-chloro-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

Di-tert-butyl {[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (150 mg) prepared in a similar manner according to Step 5 of Production Example 18 was dissolved in methanol (1.5 ml) and tetrahydrofuran (3 ml) under nitrogen atmosphere. Then N-chlorosuccinimide (59.7 mg) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 29 hours, and diluted in ethyl acetate. The organic solution was washed with saturated sodium hydrogen carbonate solution, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give di-tert-butyl {[(4-{2-[2-(acetylamino)-5-chloro-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (111 mg) as an off-white solid.

mp. 220-221°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.13(3H, s), 2.81-2.94(4H, m), 7.15(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 9.95(1H, brs), 11.43(1H, brs), 12.38(1H, brs).

MS: 538(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 82-84°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.14(3H, s), 2.82-2.97(4H, m), 7.14(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.42(3H, brs), 9.85(1H, brs), 12.38(1H, brs).

MS: 338(M+H)$^+$ free

Production Example 21: Synthesis of N-(4-{2-[4-({[amino(imino)methyl]amino}methyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride

Step 1

A mixture of N-(4-{2-[4-(aminomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (20 mg) prepared in a similar manner according to Production Example 12, N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (23 mg) and tetrahydrofuran (0.5 ml) was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica-gel with chloroform as an eluent. The crystalline residue was collected and washed with diisopropyl ether to give di-tert-butyl{[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl)amino]methylidene}biscarbamate (22 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.47(9H, s), 1.50(9H, s), 2.24(3H, s), 2.87-3.03(4H, m), 6.50(1H, s), 7.13(2H, d, J=7Hz), 7.22(2H, d, J=7Hz).

MS (M+H)=518

Step 2

A mixture of di-tert-butyl{[(4-{2-[2-(acetylamino)-1,3-

thiazol-4-yl]ethyl}benzyl)amino]methylidene}biscarbamate (20 mg), dichloromethane (2 drops) and 4N hydrogen chloride in 1,4-dioxane (0.5 ml) was stirred for 15 hours. The precipitated crystals were filtered and washed with 1,4-dioxane to give N-(4-{2-[4-({[amino(imino)methyl]amino}-methyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (13 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.80-3.00(4H, m), 4.32(2H, d, J=7Hz), 6.73(1H, s), 7.20(4H, s), 8.04(1H, t, J=7Hz).

MS (M+H)=318

Production Example 22: Synthesis of ethyl 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazole-5-carboxylate hydrochloride

Step 1

Ethyl 4-chloro-3-oxobutanoate (35 g) was dissolved in dichloromethane (70 ml), and then sulfuryl chloride (17.1 ml) in dichloromethane (20 ml) was added dropwise to the solution at 0°C over 15 minutes under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 hours, and concentrated *in vacuo*. The residual oil, N'-((E)-ethanoyl)carbamimidothioic acid (25.1 g) and acetone (600 ml) were combined. The reaction mixture was refluxed for 2.5 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. The residual solid was washed with water and isopropyl ether to give ethyl 2-(acetylamino)-4-(chloromethyl)-1,3-thiazole-5-carboxylate (21.2 g) as a pale yellow solid.

mp. 164-165°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.30(3H, t, J=7.0Hz), 2.19(3H, s), 4.29(2H, q, J=7.0Hz), 5.00(2H, s), 12.72(1H, s).

MS: 263$(M+H)^+$

Step 2: ethyl 2-(acetylamino)-4-[(E)-2-(4-

nitrophenyl)ethenyl]-1,3-thiazole-5-carboxylate

To a stirring solution of ethyl 2-(acetylamino)-4-(chloromethyl)-1,3-thiazole-5-carboxylate (1.0 g, 3.81 mmol) in N,N-dimethylformamide (20 mL) was added triphenylphosphine (1.2 g, 4.57 mmol) at room temperature. The resultant mixture was stirred at 65°C for 5 hours. To the mixture was added potassium tert-butoxide (555 mg, 4.95 mmol) at 5°C, and the resultant mixture was stirred at 5°C for 30 minutes. p-Nitrobenzaldehyde (805 mg, 5.33 mmol) was added at 5°C. After stirring for 1 hour at room temperature, the reaction was quenched with water, and the mixture was filtered to give the title compound (1.0 g, 72.7%) as a yellow solid.
^{1}H-NMR ($CDCl_3$), δ (ppm): 1.40(3H, t, J=7.2Hz), 2.33(3H, s), 4.38(2H, q, J=7.2Hz), 7.59(1H, d, J=16.0Hz), 7.70(2H, d, J=8.8Hz), 8.18(1H, d, J=16.0Hz), 8.22(2H, d, J=8.8Hz), 8.90(1H, m).

Step 3

Ethyl 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxylate was prepared in a similar manner according to Step 6 of Production Example 1.
^{1}H-NMR ($CDCl_3$), δ (ppm): 1.35(3H, t, J=7.0Hz), 2.27(3H, s), 2.84(2H, m), 3.28(2H, m), 3.56(2H, m), 4.31(2H, q, J=7.0Hz), 6.61(2H, d, J=8.3Hz), 7.01(2H, d, J=8.3Hz), 9.12(1H, m).

Step 4

Ethyl 2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}-amino)phenyl]ethyl}-1,3-thiazole-5-carboxylate was prepared in a similar manner according to Step 5 of Production Example 18.
^{1}H-NMR ($CDCl_3$), δ (ppm): 1.36(3H, t, J=7.4Hz), 1.49(9H, s), 1.53(9H, s), 2.25(3H, s), 2.94(2H, m), 3.34(2H, m), 4.31(2H, q, J=7.4Hz), 7.15(2H, d, J=8.4Hz), 7.41(2H, d, J=8.4Hz), 9.69(1H, m), 10.20(1H, s), 11.63(1H, s).

Step 5

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.28(3H, t, J=7.0Hz), 2.18(3H, s), 2.94(2H, m), 3.28(2H, m), 4.23(2H, q, J=7.0Hz), 7.16(2H, d, J=8.4Hz), 7.29(2H, d, J=8.4Hz), 7.37(3H, s), 9.71(1H, s), 12.55(1H, s).

Production Example 23: Synthesis of N-{4-[2-(4-{[(ethylamino)(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

The title compound was prepared in a similar manner according to Production Example 19.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.13(3H, t, J=6Hz), 2.11(3H, s), 2.70-3.00(6H, m), 6.70(1H, s), 6.77(2H, d, J=7Hz), 7.17(2H, d, J=7Hz).

MS (M+H)=332

Production Example 24: Synthesis of benzyl 4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-carbamate

Step 1

To an ice-cold mixture of ethyl 2-amino-1,3-thiazole-4-carboxylate (5 g), pyridine (3.36 ml) and dichloromethane (50 ml) was added benzyloxycarbonyl chloride (3.1 ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was washed with saturated aqueous sodium hydrogen bicarbonate (30 ml), dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected and washed with diisopropyl ether to give ethyl 2-{[(benzyloxy)carbonyl]amino}-1,3-thiazole-4-carboxylate (5.1 g).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.48(3H, t, J=7Hz), 4.38(2H, q, J=7Hz), 5.27(2H, s), 7.36-7.44(5H, m), 7.82(1H, s).

MS (M+H)=307

Step 2

Benzyl 4-(hydroxymethyl)-1,3-thiazol-2-ylcarbamate was prepared in a similar manner according to Step 2 of Production Example 6.

^{1}H-NMR ($CDCl_3$), δ (ppm): 4.56(2H, s), 5.27(2H, s), 6.80(1H, s), 7.30-7.46(5H, m).

MS (M+H)=265

Step 3

Benzyl 4-formyl-1,3-thiazol-2-ylcarbamate was prepared in a similar manner according to Step 3 of Production Example 6.

^{1}H-NMR ($CDCl_3$), δ (ppm): 5.29(2H, s), 7.35-7.45(5H, m), 7.81(1H, s), 9.80(1H, s).

MS (M+H)=263

Step 4

Benzyl 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-ylcarbamate was prepared in a similar manner according to Step 4 of Production Example 6.

^{1}H-NMR (DMSO-d_6), δ (ppm): 5.23(2x3/5H, s), 5.25(2x2/5H, s), 6.56-6.70(1H, m), 7.23(1H, s), 7.30-7.50(5H, m), 7.82(2x2/5H, d, J=7Hz), 7.92(2x3/5H, d, J=7Hz), 8.14(2x3/5H, d, J=7Hz), 8.21(2x2/5H, d, J=7Hz).

MS (M+H)=382

Step 5

A mixture of benzyl 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-ylcarbamate (1.4 g), palladium on carbon (140 mg) and methanol (2 ml) was stirred under hydrogen atmosphere (4 atm) at ambient temperature for 8 hours. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give benzyl 4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-ylcarbamate (1.2 g).

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.77-2.90(4H, m), 5.22(2H, s), 6.43(1H, s), 6.60(2H, d, J=7Hz), 6.92(2H, d, J=7Hz), 7.32-7.40(5H, m).

MS (M+H)=354

Step 6

A mixture of benzyl 4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-ylcarbamate (25 mg), cyanamide (6.0 mg), 4N hydrogen chloride in ethyl acetate (0.018 ml) and ethanol (1 ml) was stirred at 100°C for 72 hours. The reaction mixture was concentrated *in vacuo*. To the residue were added ethyl acetate (5 ml) and saturated aqueous sodium hydrogen bicarbonate (5 ml). The precipitated solid was filtered and washed with ethylacetate and water to give benzyl 4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-carbamate (15 mg).

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.63-2.75(4H, m), 5.07(2H, s), 6.40(1H, s), 6.94(2H, d, J=7Hz), 7.25-7.40(7H, m).

MS (M+H)=396

Production Example 25: Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}benzamide hydrochloride

Step 1

Benzyl 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-ylcarbamate (2.7 g) prepared in a similar manner according to Step 4 of Production Example 24 and 6N hydrochloric acid (50 ml) were combined. The reaction mixture was refluxed for 3 hours. After cooled to room temperature, the precipitate was filtered *in vacuo*. The solid was washed with water and acetonitrile to give 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-amine (1.34 g) as a yellow solid.

mp. 278-278.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 7.02(1H, s), 7.33(2H, s), 7.77(2H, d, J=8.5Hz), 8.25(2H, d, J=8.5Hz).

MS: 248$(M+H)^+$

Step 2

4-[(E)-2-(4-Nitrophenyl)ethenyl]-1,3-thiazol-2-amine (300 mg) and N,N-dimethylaniline (4 ml) were combined under

nitrogen atmosphere, and then benzoyl chloride (0.31 ml) was added dropwise to the suspension. The reaction mixture was stirred at 110°C for 2 hours. After cooled to room temperature, the mixture was diluted with ethyl acetate. The organic solution was washed with 1N hydrochloric acid, water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}benzamide (298.6 mg) as a yellow solid.

mp. 224.5-225°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 7.40(1H, d, J=16.0Hz), 7.45(1H, s), 7.53(1H, d, J=16.0Hz), 7.56(2H, t, J=7.0Hz), 7.66(1H, t, J=7.0Hz), 7.84(2H, d, J=8.5Hz), 8.13(2H, d, J=7.0Hz), 8.23(2H, d, J=8.5Hz), 12.80(1H, brs).

MS: 352(M+H)$^+$

Step 3

N-{4-[2-(4-Aminophenyl)ethyl]-1,3-thiazol-2-yl}benzamide was prepared in a similar manner according to Step 2 of Production Example 9.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.82(4H, s), 3.57(2H, brs), 6.53(1H, s), 6.61(2H, d, J=8.0Hz), 6.92(2H, d, J=8.0Hz), 7.50(2H, t, J=7.0Hz), 7.60(1H, t, J=7.0Hz), 7.93(2H, d, J=7.0Hz), 10.15(1H, brs).

MS: 324(M+H)$^+$

Step 4

Di-tert-butyl {[(4-{2-[2-(benzoylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 5 of Production Example 18.

mp. 143-144°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.95(4H, s), 6.86(1H, s), 7.22(2H, d, J=8.5Hz), 7.44(2H, d, J=8.5Hz),

7.54(2H, t, J=7.5Hz), 7.63(1H, t, J=7.5Hz), 8.10(2H, d, J=7.5Hz), 9.94(1H, s), 11.44(1H, brs), 12.66(1H, brs).

MS: 566(M+H)$^+$

Step 5

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 229-232°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.91-3.05(4H, m), 6.88(1H, s), 7.15(2H, d, J=8.5Hz), 7.32(2H, d, J=8.5Hz), 7.44(3H, brs), 7.54(2H, t, J=7.5Hz), 7.64(1H, t, J=7.5Hz), 8.10(2H, d, J=7.5Hz), 9.88(1H, s).

MS: 366(M+H)$^+$ free

Production Example 26: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

4-(Methylsulfanyl)benzaldehyde (31.8 g), (acetylamino)acetic acid (24.5 g) and acetic anhydride (35 ml) were combined, and then sodium acetate (8.57 g) was added to the suspension at room temperature under nitrogen atmosphere. The reaction mixture was refluxed for 3.5 hours. After cooled to room temperature, the mixture was poured into ice-water and ethyl acetate with stirring, and filtered *in vacuo*. The filtrate was separated. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue and the previously obtained solid were combined, and the mixture was purified by flash column chromatography over silica gel with chloroform / ethyl acetate (30:1) as an eluent, and triturated with isopropyl ether to give (4Z)-2-methyl-4-(4-(methylsulfanyl)benzylidene)-1,3-oxazol-5(4H)-one (17.8 g) as a brown solid.

mp. 154-155°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.38(3H, s), 2.53(3H, s), 7.19(1H, s), 7.36(2H, d, J=8.5Hz), 8.12(2H, d, J=8.5Hz).

Step 2

(4Z)-2-Methyl-4-(4-(methylsulfanyl)benzylidene)-1,3-oxazol-5(4H)-one (17.5 g), 1,4-dioxane (100 ml) and 4N-hydrochloric acid (27 ml) were combined. The reaction mixture was refluxed for 3 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. Ethyl acetate and water were added to the residue, and the precipitate was filtered *in vacuo* to give 3-(4-(methylsulfanyl)phenyl)-2-oxopropanoic acid (6.7 g) as a pale brown solid.

mp. 165-167°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.48(3H, s), 6.37(1H, s), 7.23(2H, d, J=8.5Hz), 7.70(2H, d, J=8.5Hz), 9.44(1H, s).

MS: 209$(M-H)^+$

Step 3

3-(4-(Methylsulfanyl)phenyl)-2-oxopropanoic acid (16.2 g), N,N-dimethylformamide (81 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (11.5 ml) were combined at 0°C under nitrogen atmosphere. The mixture was stirred at the same temperature for an hour, and then iodomethane (9.59 ml) was added to the solution at the same temperature. The reaction mixture was stirred at room temperature for 4 hours, poured into 1N-hydrochloric acid, and extracted with ethyl acetate (twice). The combined organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / ethyl acetate (30:1) as an eluent, and triturated with isopropyl ether / n-hexane to give methyl 3-(4-(methylsulfanyl)phenyl)-2-oxopropanoate (8.6 g) as a dark yellow solid.

mp. 112-113°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.48(3H, s), 3.79(3H, s), 6.41(1H, s), 7.24(2H, d, J=8.5Hz), 7.72(2H, d, J=8.5Hz), 9.52(1H, brs).

MS: 223(M-H)$^+$

Step 4

Methyl 3-(4-(methylsulfanyl)phenyl)-2-oxopropanoate (2.84 g), pyridinium tribromide (4.95 g), dichloromethane (140 ml) and acetic acid (0.5 ml) were combined at 0°C under nitrogen atmosphere. The reaction mixture was stirred at 0°C for 2 hours, and poured into water. The mixture was extracted with ethyl acetate (twice). The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual oil was dissolved in ethanol (55 ml), and then thiourea (1.25 g) was added to the solution. The reaction mixture was refluxed for 1 hour under nitrogen atmosphere. After cooled to 0°C, water was added to the solution. The precipitate was filtered *in vacuo* to give methyl 2-amino-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (2.67 g) as a brown solid.

mp. 184-185°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.50(3H, s), 3.64(3H, s), 7.25(2H, d, J=8.5Hz), 7.34(2H, d, J=8.5Hz).

MS: 281(M+H)$^+$

Step 5

Methyl 2-amino-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (8.8 g) was dissolved in pyridine (88 ml), and then acetyl chloride (6.7 ml) was added dropwise to the solution at 0°C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 minutes and at 50°C for 2 hours. After cooled to 0°C, water was added to the solution. The precipitate was filtered *in vacuo*, and the solid was washed with ethyl ether to give methyl 2-(acetylamino)-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (9.3 g) as

an off-white solid.

mp. 253-254.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.52(3H, s), 3.70(3H, s), 7.30(2H, d, J=8.5Hz), 7.44(2H, d, J=8.5Hz).

MS: 323$(M+H)^+$

Step 6

Methyl 2-(acetylamino)-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (200 mg) was dissolved in tetrahydrofuran (2 ml), and then lithium aluminium hydride (35.3 mg) was added portionwise to the solution at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 30 minutes, and quenched with methanol. Ethyl acetate and 1N hydrochloric acid were added to the mixture, and extracted. The aqueous layer was extracted with ethyl acetate (twice). The combined organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was dissolved in methanol (0.4 ml) and chloroform (7 ml). Then manganase (IV) oxide (1.08 g) was added to the solution under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 13 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give N-{4-formyl-5-[4-(methylthio)phenyl]-1,3-thiazol-2-yl}acetamide (153.6 mg) as a pale brown amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 2.54(3H, s), 7.38(2H, d, J=8.5Hz), 7.58(2H, d, J=8.5Hz), 9.77(1H, s), 12.59(1H, brs).

MS: 293$(M+H)^+$

Step 7

N-{5-[4-(Methylthio)phenyl]-4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide was prepared

in a similar manner according to Step 1 of Production Example 9.

mp. 228-230°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.19(3H, s), 2.54(3H, s), 7.32(1H, d, J=16.0Hz), 7.40(2H, d, J=8.5Hz), 7.46(1H, d, J=16.0Hz), 7.47(2H, d, J=8.5Hz), 7.79(2H, d, J=9.0Hz), 8.19(2H, d, J=9.0Hz), 12.38(1H, brs).

MS: 412(M+H)$^+$

Step 8

Potassium peroxymonosulfate (408 mg) was suspended in water (1 ml) and tetrahydrofuran (1 ml), and then N-{5-[4-(methylthio)phenyl]-4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (182 mg) in tetrahydrofuran (3 ml) was added dropwise to the suspension at 0°C. The reaction mixture was stirred at room temperature for 2 hours, and then water was added to the suspension. The precipitate was filtered *in vacuo*. The solid was washed with water and ethyl acetate to give N-{5-[4-(methylsulfonyl)phenyl]-4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (83 mg) as a yellow solid.

mp. 294-295°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.21(3H, s), 3.30(3H, s), 7.40(1H, d, J=16.0Hz), 7.54(1H, d, J=16.0Hz), 7.82(2H, d, J=8.5Hz), 7.84(2H, d, J=8.5Hz), 8.05(2H, d, J=8.5Hz), 8.20(2H, d, J=8.5Hz), 12.51(1H, brs).

MS: 442(M-H)$^+$

Step 9

N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 2 of Production Example 9.

mp. 202-204°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.77-2.88(4H, m),

3.24(3H, s), 6.84(2H, brs), 6.45(2H, d, J=8.5Hz), 6.77(2H, d, J=8.5Hz), 7.49(2H, d, J=8.5Hz), 7.91(2H, d, J=8.5Hz), 12.34(1H, brs).

MS: 416(M+H)$^+$

Step 10

Di-tert-butyl {[(4-{2-[2-(acetylamino)-5-(4-(methylsulfonyl)phenyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 5 of Production Example 18.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.17(3H, s), 2.97(4H, s), 3.24(3H, s), 7.11(2H, d, J=8.5Hz), 7.38(2H, d, J=8.5Hz), 7.56(2H, d, J=8.5Hz), 7.92(2H, d, J=8.5Hz), 9.92(1H, s), 11.43(1H, brs), 12.34(1H, brs).

MS: 658(M+H)$^+$

Step 11

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 145-146.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 2.99(4H, brs), 3.25(3H, s), 7.11(2H, d, J=8.0Hz), 7.22(2H, d, J=8.0Hz), 7.38(3H, brs), 7.57(2H, d, J=8.0Hz), 7.94(2H, d, J=8.0Hz), 9.79(1H, s), 12.36(1H, brs).

MS: 458(M+H)$^+$ free

Production Example 27: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-methyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Ethyl 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxylate (310 mg) prepared in a similar manner according to Step 3 of Production Example 22 was dissolved in tetrahydrofuran (6 ml) under nitrogen atmosphere. Then di(tert-butyl)dicarbonate (223 mg) in tetrahydrofuran (1 ml) was added to the solution at room temperature. The reaction

mixture was refluxed for 2 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. The residual solid was washed with ethyl ether to give ethyl 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}-ethyl)-1,3-thiazole-5-carboxylate (370.7 mg) as an off-white solid.

mp. 213-214°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.26(3H, t, J=7.0Hz), 1.46(9H, s), 2.17(3H, s), 2.85(2H, t, J=7.5Hz), 3.23(2H, t, J=7.5Hz), 4.22(2H, q, J=7.0Hz), 7.04(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 9.23(1H, brs), 12.55(1H, brs).

MS: 434$(M+H)^+$

Step 2

Ethyl 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)-amino]phenyl}ethyl)-1,3-thiazole-5-carboxylate (3 g), 1N-aqueous sodium hydroxide solution (17.3 ml) and ethanol (30 ml) were combined, and the mixture was refluxed for 5 hours. After cooled to room temperature, the organic solvent was removed *in vacuo*. The aqueous solution was acidified (pH=4) with 1N-hydrochloric acid, and extracted with ethyl acetate (twice). The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was dissolved in pyridine (45 ml), and then acetyl chloride (1.48 ml) was added dropwise to the solution at 0°C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 13 hours, and pyridine was removed *in vacuo*. Water was added to the residue, and acidified with 1N-hydrochloric acid. The precipitate was collected *in vacuo*. The solid was washed with water and ethyl ether to give 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)-amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (2.23 g) as an off-white solid.

mp. 237-238°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.16(3H, s), 2.85(2H, m), 3.23(2H, m), 7.04(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 9.24(1H, s), 12.46(1H, s).

MS: 404(M-H)$^+$

Step 3

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (80 mg), 30% methylamine in ethanol solution (0.02 ml), 1-hydroxybenzotriazole (29.3 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (39.7 mg) in dichloromethane (1 ml) and N,N-dimethylformamide (0.5 ml) was stirred at ambient temperature for 20 hours. The reaction mixture was poured into saturated sodium hydrogen carbonate solution, and extracted with chloroform. The organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give tert-butyl 4-(2-{2-(acetylamino)-5-[(methylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenylcarbamate (92.8 mg) as an off-white amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.69(3H, d, J=4.5Hz), 2.78-2.86(2H, m), 3.12-3.20(2H, m), 7.06(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.91(1H, q, J=4.5Hz), 9.22(1H, brs), 12.34(1H, brs).

MS: 419(M+H)$^+$

Step 4

tert-Butyl 4-(2-{2-(acetylamino)-5-[(methylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenylcarbamate (95 mg) and trifluoroacetic acid (2 ml) were combined at 0°C. The reaction mixture was stirred at room temperature for an hour, and concentrated *in vacuo*. The residue was dissolved in chloroform. The organic solution was washed with 1N sodium hydroxide solution, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and

concentrated *in vacuo*. The residue was purified by preparative silica gel column chromatography with chloroform / methanol (10:1) as an eluent to give 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-methyl-1,3-thiazole-5-carboxamide (49 mg) as an off-white amorphous substance.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 2.68(3H, d, J=4.5Hz), 2.67-2.75(2H, m), 3.05-3.15(2H, m), 4.83(2H, brs), 6.47(2H, d, J=8.5Hz), 6.84(2H, d, J=8.5Hz), 7.85(1H, q, J=4.5Hz), 12.33(1H, brs).

MS: 319(M+H)$^+$

Step 5

Di-tert-butyl {[(4-{2-[2-(acetylamino)-5-(methylaminocarbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]-methylidene}biscarbamate was prepared in a similar manner according to Step 5 of Production Example 18.

mp. 245-246°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.40(9H, s), 1.51(9H, s), 2.14(3H, s), 2.68(3H, d, J=4.5Hz), 2.85-2.94(2H, m), 3.14-3.25(2H, m), 7.17(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 7.88(1H, q, J=4.5Hz), 9.94(1H, s), 11.44(1H, brs), 12.38(1H, brs).

MS: 561(M+H)$^+$

Step 6

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 101-104°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.67(3H, d, J=4.5Hz), 2.86-2.96(2H, m), 3.16-3.26(2H, m), 7.14(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz), 7.41(3H, brs), 7.99(1H, q, J=4.5Hz), 9.81(1H, s), 12.36(1H, brs).

MS: 361(M+H)$^+$ free

Production Example 28: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-phenyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (80 mg), aniline (0.019 ml), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (113 mg) and N,N-diisopropylethylamine (0.076 ml) in N,N-dimethylformamide (2 ml) was stirred at ambient temperature for 21 hours and at 55°C for 3 hours. The reaction mixture was poured into 1N hydrochloric acid, and extracted with chloroform. The organic layer was washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give tert-butyl 4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-thiazol-4-yl]ethyl}phenylcarbamate (57.2 mg) as a colorless solid.

mp. 199-200°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.18(3H, s), 2.81-2.91(2H, m), 3.14-3.24(2H, m), 7.05(2H, d, J=8.5Hz), 7.08(1H, t, J=8.5Hz), 7.26-7.36(4H, m), 7.64(2H, d, J=8.5Hz), 9.22(1H, brs), 9.95(1H, brs), 12.44(1H, brs).

MS: 481(M+H)$^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-phenyl-1,3-thiazole-5-carboxamide was prepared from tert-butyl 4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-thiazol-4-yl]ethyl}phenylcarbamate in a similar manner according to Step 4 of Production Example 27.

mp. 104-105°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 2.71-2.81(2H, m), 3.09-3.18(2H, m), 5.07(2H, brs), 6.48(2H, d, J=8.0Hz), 6.85(2H, d, J=8.0Hz), 7.08(1H, t, J=8.0Hz), 7.33(2H, t, J=8.0Hz), 7.65(2H, d, J=8.0Hz), 9.93(1H, brs), 12.44(1H, brs).

MS: 381(M+H)$^+$

Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-phenyl-1,3-thiazole-5-carboxamide in a similar manner according to Step 5 of Production Example 18.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.18(3H, s), 2.87-2.98(2H, m), 3.17-3.29(2H, m), 7.08(1H, t, J=8.0Hz), 7.16(2H, d, J=8.5Hz), 7.31(2H, t, J=8.0Hz), 7.41(2H, d, J=8.5Hz), 7.64(2H, d, J=8.0Hz), 9.93(2H, s), 11.43(1H, brs), 12.46(1H, brs).

MS: 623(M+H)$^+$

Step 4

The title compound was prepared from di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate in a similar manner according to Step 6 of Production Example 27.

mp. 152-155°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.19(3H, s), 2.90-3.01(2H, m), 3.17-3.29(2H, m), 7.09(1H, t, J=8.0Hz), 7.13(2H, d, J=8.0Hz), 7.26(2H, d, J=8.0Hz), 7.33(2H, t, J=8.0Hz), 7.40(3H, brs), 7.64(2H, d, J=8.0Hz), 9.79(1H, s), 10.02(1H, s), 12.46(1H, s).

MS: 423(M+H)$^+$ free

Production Example 29: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N,N-dimethyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl [4-(2-{2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate was prepared from the compound of Step 2 of Production Example 27 in a similar manner according

to Step 3 of Production Example 27.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.14(3H, s), 2.84(4H, s), 2.85(6H, s), 7.01(2H, d, J=8.5Hz), 7.31(2H, d, J=8.5Hz), 9.21(1H, brs), 12.33(1H, brs).

MS: 433(M+H)$^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N,N-dimethyl-1,3-thiazole-5-carboxamide was prepared from tert-butyl [4-(2-{2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate in a similar manner according to Step 4 of Production Example 27.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.14(3H, s), 2.70-2.77(4H, m), 2.86(6H, s), 4.83(2H, s), 6.45(2H, d, J=8.5Hz), 6.78(2H, d, J=8.5Hz), 12.32(1H, brs).

MS: 333(M+H)+

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N,N-dimethyl-1,3-thiazole-5-carboxamide in a similar manner according to Step 5 of Production Example 18.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.14(3H, s), 2.85(6H, s), 2.89(4H, s), 7.12(2H, d, J=8.5Hz), 7.40(2H, d, J=8.5Hz), 9.92(1H, s), 11.43(1H, brs), 12.36(1H, brs).

MS: 575(M+H)$^+$

Step 4

The title compound was prepared from di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate in a similar manner according to Step 6 of Production Example 27.

mp. 78-80°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 2.81-2.96(4H, m),

2.88(6H, s), 7.11(2H, d, J=8.5Hz), 7.18(2H, d, J=8.5Hz), 7.38(3H, brs), 9.77(1H, s), 12.34(1H, s).

MS: 375(M+H)$^+$ free

Production Example 30: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-benzyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl [4-(2-{2-(acetylamino)-5-[(benzylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate was prepared from the compound of Step 2 of Production Example 27 in a similar manner according to Step 3 of Production Example 27.

mp. 184-185°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.79-2.87(2H, m), 3.12-3.22(2H, m), 4.37(2H, d, J=6.5Hz), 7.02(2H, d, J=8.5Hz), 7.18-7.36(7H, m), 8.56(1H, t, J=6.5Hz), 9.22(1H, brs), 12.37(1H, brs).

MS: 495(M+H)$^+$

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-benzyl-1,3-thiazole-5-carboxamide was prepared from tert-butyl [4-(2-{2-(acetylamino)-5-[(benzylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate in a similar manner according to Step 4 of Production Example 27.

mp. 200-201°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 2.66-2.76(2H, m), 3.07-3.15(2H, m), 4.38(2H, d, J=6.0Hz), 4.83(2H, s), 6.46(2H, d, J=8.5Hz), 6.81(2H, d, J=8.5Hz), 7.20-7.36(5H, m), 8.52(1H, t, J=6.0Hz), 12.32(1H, brs).

MS: 395(M+H)$^+$

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(benzylamino)carbonyl]-1,3-thiazol-4-

yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-benzyl-1,3-thiazole-5-carboxamide in a similar manner according to Step 5 of Production Example 18.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.85-2.94(2H, m), 3.16-3.25(2H, m), 4.37(2H, d, J=6.0Hz), 7.12(2H, d, J=8.5Hz), 7.22-7.36(5H, m), 7.40(2H, d, J=8.5Hz), 8.32(1H, s), 8.54(1H, t, J=6.0Hz), 9.94(1H, brs), 11.44(1H, brs).

MS: 637 $(M+H)^+$

Step 4

The title compound was prepared from di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(benzylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate in a similar manner according to Step 6 of Production Example 27.

mp. 128-130°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.17(3H, s), 2.85-2.96(2H, m), 3.16-3.27(2H, m), 4.36(2H, d, J=6.0Hz), 7.12(2H, d, J=8.5Hz), 7.17-7.35(7H, m), 7.40(3H, brs), 8.66(1H, t, J=6.0Hz), 9.78(1H, s), 12.38(1H, s).

MS: 437 $(M+H)^+$ free

Production Example 31: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide hydrochloride

Step 1

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (100 mg), (4-nitrobenzyl)amine hydrochloride (46.5 mg), 1-hydroxybenzotriazole (36.7 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (40.2 mg) in DMF (2 ml) was stirred at ambient temperature for 73 hours. The reaction mixture was poured into saturated $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with water and brine,